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DIFFERENTIATION AS EFFECTED BY DIIODO-TYROSINE PLUS CERTAIN OTHER AMINO ACIDS*

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The amino acid requirements of young as well as of mature organisms, mainly the mammalian, have been studied from various angles. So-called "incomplete" proteins, lacking one or more essential amino acids, have been used for feeding, and, then again, various combinations of isolated acids have been supplied in the diet. It was recognized early that definite minimum amounts of certain amino acids are required for satisfactory maintenance and that some acids facilitate growth. There have also appeared a few reports (Abderhalden, Emery, McCarrison, Pincherle, etc.) on observations on organisms lower in the phylogenetic scale than the mammals.

A few years ago we began to study growth and differentiation processes on amphibian larvae kept on a diet in which an amino acid, or mixtures of amino acids, act as the sole source of N. Our problem is to determine whether or not it is possible for organisms (1) to maintain themselves, (2) to grow, (3) to differentiate—on one, two, three or more amino acids, and whether or not there is any potential difference between the acids, as far as their value for maintenance or/and growth or/and differentiation is concerned. The acids are given, in various concentrations from 1:1000 up, dissolved in the tap water in which the animals are being reared, the non-nitrogenous "basal diet" consisting of dextrose, sucrose, cod liver oil and lemon juice.

The details of these experiments are being reported elsewhere. The purpose of this paper is to report on one particular phase of our work because it deals with those amino acids which bear structural relationship to some hormones. Our experiments have shown that some amino acids are sufficient for the maintenance of tadpoles; that others of a more complex structure are of influence, if not actually required, in the growth process; and finally, that others, still more complex and of a structure which ap-

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proaches that of diiodo-tyrosine (and thyroxine) are of definite influence in the process of differentiation. Those of the last type, viz., "differentiation" acids, are the aromatic ring acids, phenyl-alanine, tyrosine and tryptophane.

In the course of our experiments it became evident that animals which were fed on one or more of these acids, either alone or in combination with acids of a different structure, showed a more rapid and a more complete course of differentiation than when these acids were lacking in the diet. The following figures will illustrate this point. In one type of experiment the animals were arranged in groups of 20, several groups (in this particular experiment, 13) making up one set. Signs of differentiation occurred as follows:

(a) "Differentiation" acids:

In the phenyl-alanine set.....in 50% of the groups
In the tyrosine set.....in 65% of the groups
In the tryptophane set.....in 46% of the groups

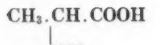
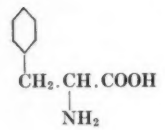
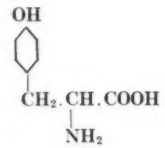
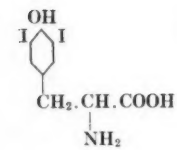
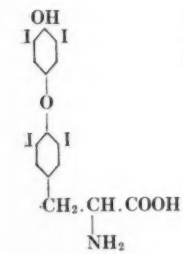
(b) "Non-differentiation" acids:

In the glycine set.....in 16.5% of the groups
In the arginine set.....in 10.0% of the groups
In the cystine set.....in 18.2% of the groups

It must be pointed out here that not only was the number of groups showing signs of differentiation much higher in (a) than in (b), but the extent of differentiation, likewise, was much greater. Some animals in (a) would reach almost the last stages of differentiation, just before metamorphosis, while the animals in (b) would show little more than the first signs of hind limb development.

Similar observations were made in other experiments in which the acids were grouped in various combinations. It would seem, therefore, that an essential differentiation factor is contained in the three acids: phenyl-alanine, tyrosine and tryptophane, and perhaps also in the simple, straight chain acid, alanine, from which the others are derived. As this differentiation factor is definitely present in the more complex iodinated acids, diiodo-tyrosine and thyroxine, it seemed desirable to compare the effectiveness of the three acids with that of diiodo-tyrosine (resp. thyroxine) and to ascertain in particular whether or not any one of the three acids is capable of altering, probably of augmenting, the accelerating influence of diiodo-tyrosine (resp. thyroxine). This question can now be answered in the affirmative.

The chemical relationship of the several acids can be seen from the structural formulae. The series shows a progressive complexity of structure, with an increase of molecular weight, and with the progressive complexity goes parallel an increasing degree of effectiveness in differentiation, the final thyroid hormone, thyroxine, being the strongest catalyst in the series.

	**ALANINE** α—amino-propionic acid	Molecular weight 89
	**PHENYL-ALANINE** β—phenyl—α—amino-propionic acid	165
	**TYROSINE** β—para-hydroxy-phenyl—α—amino-propionic acid	181
	TRYPTOPHANE β—indol—α—amino-propionic acid	204
	**DIIODO-TYROSINE** 3,5—diiodo—4—hydroxy-phenyl—α—amino-propionic acid	433
	**THYROXINE** β[3′, 5′—diiodo—4′—(3, 5 diiodo—4—hydroxyphenoxy)—phenyl]—α—amino-propionic acid	777

The records of a few experiments may now be given. Each plus (+) marks the appearance of a somatic feature which indicates the degree of differentiation, six or seven (+) marking the last stages before the completion of metamorphosis. The somatic criteria are: appearance of hind limbs, change in body shape, change in mouth-parts, appearance of fore-limbs, beginning tail absorption, etc.

The chart shows that animals receiving diiodo-tyrosine plus a differentiation acid reach the final stages of metamorphosis earlier than other groups. Tryptophane plus diiodo-tyrosine, each in 1:1000 concentration, accelerates differentiation almost as much as diiodo-tyrosine, 1:1000, alone; tyrosine following close behind, phenyl-alanine being the weakest of the three "differentiation" acids.

In evaluating this experiment, it should be remembered that the "differentiation" acids were the last ones to be introduced into the series, thus occupying seventh, eighth and ninth positions, respectively. The concentrations in which they were present were, therefore, very low, 1/7, 1/8, 1/9: 1000. Nevertheless, when diiodo-tyrosine was added, its influence became best noticeable in these groups, the tryptophane group being the first one to reach the 2+ stage and only two days later the 5+ stage. The tyrosine group was the next one to reach the 5 and 6+ stage and, aside from these two groups, no other group reached the 6+ stage. Phenyl-alanine which we consider the weakest "differentiation" acid did not seem to give much support to diiodo-tyrosine in the concentration applied (1/7:1000).

An interesting feature of the experiment is the alanine effect. It is necessary to emphasize this point, since the observation was made not only in this particular set-up, but in other series as well. Alanine, which has the basic structure of the "differentiation" acid, though without the ring nucleus, gave indications of exerting some influence on differentiation. We do not wish to be too definite in making this statement before having collected further data. At any rate, in this experiment the alanine group reached the 2+ and the 5+ stage almost as soon as the tryptophane group. The rapid advance, within 24 hours, from the 2+ to the 5+ stage is worthy of note, as such rapidity of advancement is characteristic of the "differentiation" acids.

The "growth" acid groups arginine, cystine, lysine, show a gradual response to the diiodo-tyrosine influence, the 5+ and 6+ stages being reached later than in the "differentiation" acids; e.g., in cystine and lysine seven days later than tryptophane.

In this series all acids were given in equal amounts, tyrosine, e.g., in exactly the same concentration as glycine or leucine, yet the influence of the "differentiation" acids was not as pronounced as in the previous experiment where phenyl-alanine, tryptophane and tyrosine were present in concentrations of only 1/7, 1/8, 1/9 per 1000. An observation repeatedly made by us in other sets may help to explain this discrepancy: a single acid is a very insufficient diet, while the food value of a mixture increases

I. RANA SYLVATICA. Hatched 4/2/30; first basal diet feeding, 4/7; first amino acid feeding. 4/8; first diiodotyrosine feeding, 4/10. In each case, ONE amino acid (in concentration 1:1000) plus diiodo-tyrosine (in concentration 1:1000) were used. Total acid concentration, thus, 2:1000. The last group received diiodo-tyrosine alone, in concentration 2:1000.

Diiodo-tyrosine plus	4/12	4/14	4/15	4/16	4/17	4/19	4/20	4/21	4/23	4/24	4/25	4/26	4/27	4/28	4/29
Glycine									+					++++(+)	++++++
Alanine		++				+++						++++++(+)			
Leucine		++				+++++						+++++(+)			
Aspartic Acid		++				++					+++++	+++++++			
Glutamic Acid		++										++++++			
Arginine											+++				++++++(+)
Lysine	+	++			+++									++++++(−)	
Cystine	+	++				++++								+++++(+)	
Phenyl-alanine	+(+)	++				++++				++++++(−)					
Tyrosine	+	++				++++		++++++(+)							
Tryptophane	+			++	++++	+++++	++++++								
Histidine		++						++			++++	++++++	+++++++		+++++++
Diiodo-tyrosine		++	++++(+)			+++++	++++++								

II. RANA SYLVATICA. Hatched 4/10/31. Feeding began 4/21/31. Basal diet. The first group received two acids (glycine+leucine), the second group three acids (glycine+leucine+alanine), etc., until finally the ninth acid, tyrosine, was added to the mixture. TOTAL acid concentration in every case 1:1000. The animals were allowed to develop on this diet until 6/10, from which day on diiodo-tyrosine, 1:10,000, was added to the acid mixture. Though the concentration of diiodo-tyrosine was very low, its influence became quickly noticeable, as shown in the following table:

	6/10	6/12	6/17	6/18	6/19	6/20	6/22	6/23	6/24	6/25	6/26
Glycine + Leucine		+	+	+	+++	++++	++++				
Glycine + Alanine		−	+(−)	+(+)	+++++	+++++					
Glycine + Arginine	Diiodo-	+	+	+	+++	++++(−)		+++++			
Glycine + Cystine	tyrosine	+(+)			++	++++(−)				++++++	
Glycine + Lysine	treatment	+	+	+	++(+)	++++(−)				++++++	
Glycine + Phenyl-alanine	began	+(−)	+(−)		+	++++(−)		++++	++++		
Glycine + Tryptophane		−	++	++	++++++	++++++					
Glycine + Tyrosine		+(−)		+	+	++++(+)		+++++		++++++	++++++

III. RANA SYLVATICA. Hatched 4/10/31. Feeding began 4/21/31. Basal diet plus single acids, 1:1000, were given; after 6/10, diiodo-tyrosine, 1:10,000, was added. Again the influence of the latter became noticeable very quickly, though the concentration was low.

	6/10	6/13	6/14	6/16	6/17	6/19	6/20	6/24	6/25
Glycine		−	+	++	+++	++++	++++		
Leucine		?	?	+	+++	+++	++++++		
Alanine		+ ?	+ ?	+	++				
Arginine	First	+	+	+	+	+++	+++	++++++	
Cystine	treatment	+	+	+	+				
Lysine	with	−	−	+++	++++++	+++++++	+++++++		
Phenyl-alanine	diiodo-	+	++	++	++	+++	++++++		
Tryptophane	tyrosine	+ ?	+	++	++	++++	+++++++		
Tyrosine		+	+	++	+++	++++(−)	++++++		
Histidine		+	+	+		++++(+)			+++++++

with the number of acids present. In experiment III the animals received only one acid per group, while in experiment II mixtures of acids were given. The latter animals, therefore, were in a better state of nutrition and more advanced in development on the day when diiodo-tyrosine was introduced. Thus, they were better able to respond to the differentiation stimulus. (It is well known from thyroid and thyroxine experiments that the closer a tadpole is to normal metamorphosis, the more quickly will it be affected by the stimulus.)

Nevertheless, even in experiment III the influence of the "differentiation" acids supporting that of diiodo-tyrosine was noticeable. The phenyl-alanine group was the first one to reach the 2+ stage, 3+ and 4+ appear a few days later. The tryptophane group reached 7+ within ten days after the introduction of diiodo-tyrosine, while phenyl-alanine and tyrosine were only a little behind. Comparisons with the other acids can be made from the table. The lysine group, though lacking in quick initial response, reacted very strongly to diiodo-tyrosine and reached 7+ one day sooner than tryptophane. Lysine being a growth acid, the size of the animals which was large in comparison with that of the differentiation acids may have been a factor favorable for differentiation.

The record of another series, IV, also gives indication of a tendency of the "differentiation" acids to accelerate the rate of development and of the support which they give to diiodo-tyrosine. In this series, the animals at first were kept on two-acid mixtures, every acid being paired with every other; on 7/19 diiodo-tyrosine was added. Of the groups which received at least one differentiation acid in the two acid mixtures, 50 per cent showed signs of differentiation before 7/19, of the groups receiving no such acid only 20 per cent showed signs of differentiation. The addition, on 7/19, of diiodo-tyrosine to the two-acid mixtures emphasized this divergence still further.

Above the cross line are grouped the "differentiation" acids, below the "non-differentiation" acids.

The number of crosses, on respective days, is preponderant above the line. On 7/22 the number of groups is also preponderant above the line, showing the striking response of the "differentiation" acid groups to diiodo-tyrosine. On 7/23 the "non-differentiation" acid groups gradually catch up with the "differentiation" acid groups, though in many of the former the number of (+) is still small, in some groups none.

An exception is made by the phenyl-alanine + phenyl-alanine group which lags a day (7/24) behind. These animals were notably small, thus not so susceptible to the differentiation factor. It must also be remembered that a time-interval of 24 hours (7/23-7/24), as it appears on the chart, does not mean that the recorded changes occurred exactly 24 hours after the previous observation. Since it was not possible to make hourly observations, the animals were examined from day to day. With more

IV. RANA SYLVATICA. Hatched 4/2/30. First feeding on 4/10/30. Basal diet plus two acids in total concentration of 1:1000. On 7/19 diiodo-tyrosine, 1:10,000, was introduced. Within two days, signs of differentiation appeared. The number of plus symbols (+) indicates the extent of differentiation.

7/19	7/21	7/22	7/23	7/24
First diiodo-tyrosine treatment	Glycine -Arginine +	Phenyl-alanine-Leucine +++	Tyrosine -Arginine +++++	*Phenyl-alanine-Phenyl-alanine ++++
	*Glycine -Cystine ++++++	Phenyl-alanine-Lysine ++	*Tyrosine -Histidine +++++	
	Glycine -Lysine ++	Phenyl-alanine-Tyrosine +++++	Tryptophane -Glycine ++++	
	Arginine -Glutamic Acid +	*Phenyl-alanine-Tryptophane ++++	Histidine -Arginine ++++	
		Phenyl-alanine-Histidine ++++++	*Histidine -Cystine +++	
		*Tyrosine -Glycine ++++		
		Tyrosine -Leucine ++++		
		Tyrosine -Aspartic Acid ++++++		
		*Tyrosine -Cystine ++++		
		Tryptophane -Leucine +		
		*Tryptophane -Histidine +++++		
		Histidine -Glycine +		
		Histidine -Alanine ++++		
		Histidine -Leucine ++++		
		*Histidine -Lysine ++++		
		*Histidine -Proline +++		
		Glycine -Glycine +++	Glycine -Alanine ++++	
		Glycine -Glutamic Acid −	Glycine -Leucine +++++	
		Alanine -Lysine +	Glycine -Aspartic Acid +	
		Aspartic Acid -Arginine ++	Glycine -Proline +	
		Aspartic Acid -Cystine +	*Alanine -Leucine ++++++	
		Leucine -Cystine +	Alanine -Cystine +++	
		*Lysine -Cystine +++++	Leucine -Leucine +++++	
		Lysine -Glutamic Acid ++	Leucine -Glutamic Acid +	
			Leucine -Arginine ++	
			Leucine -Lysine +	
			Leucine -Proline −	
			Arginine -Lysine ++	
			Arginine -Cystine −	
			Cystine -Cystine +++++	
			Cystine -Glutamic Acid +++++	
			Cystine -Proline ++	

NOTE:—* Indicates that there were signs of beginning differentiation on or shortly before 7/19.

numerous examinations, phenyl-alanine + phenyl-alanine might have fallen into the 7/23 column.

The same holds true for four "non-differentiation" acid groups on 7/21, which seem to run somewhat ahead of the others. The span 7/21-7/22 does not necessarily represent 24 hours, but may merely be the interval between a late afternoon and an early morning examination. Furthermore, each of these four groups contains at least one growth acid, thus the animals were of good size and ready for differentiation; and still further, only one of the four groups showed 6+, the others only one or two, which stages were markedly surpassed on the next day by most of the "differentiation" acids.

The evidence, thus, is in favor of the "differentiation" acids.

DISCUSSION

From the standpoint of endocrinology and in an analysis of the influence of internal secretions on development we are interested not only in the process of differentiation, but also in the process of growth. The two major phases of development occur simultaneously and interdependently, though usually not with the same degree of velocity. In early embryonic life, much differentiation occurs without accompanying growth and on the other hand at several periods in development growth must have proceeded to some extent before further differentiation can occur. Experimentally, it is possible within certain limits to separate the two processes from each other and to have development proceed more in the direction of growth or more in that of differentiation. Nature performs such experiments quite often and the many instances of accelerated and excessive growth coupled with retarded and incomplete differentiation are well known to the endocrinologist. In animal experimentation it is easier in most cases to accentuate the differentiation phase rather than the growth phase. In some instances (tadpole metamorphosis) differentiation can be forced by chemical means (thyroid, thyroxine, diiodo-tyrosine) to such an extent that no growth occurs at all. An experiment of the opposite type is the castration experiment, the result of which is retarded and incomplete somatic differentiation, while growth may continue beyond the normal time and size. Stimulation of growth by pituitary agents might also be mentioned here.

In our present experiments we are studying not only the "differentiation" acids, but also acids which primarily influence or facilitate growth. Such acids are: arginine, lysine and cystine. In mammalian experiments these acids had been shown to be "growth" acids and in our experiments, too, their value as "growth" acids is evident. At this moment we are not in a position to report more data which might be of interest to the endocrinologist about the physiological value of these acids as "growth" acids. While we know definitely that the "differentiation" acids are required for advanced differentiation, we do not yet know how essential the "growth" acids are for growth. We know that they facilitate growth and that ani-

mals treated with "growth" acids grow much better and to greater size than animals not so treated. It may be recalled here that we have still a third group of acids, "maintenance" acids, glycine, alanine and leucine, and that animals treated with such acids may be maintained in a healthy condition for quite some time without showing much growth or differentiation. Whenever a "growth" acid is added to the "maintenance" acids, growth is far better even though the absolute quantity of food has not been increased. Furthermore, we know how to link chemically the "differentiation" acids, phenyl-alanine, tryptophane, tyrosine, with the endocrine substances which are known to be responsible for differentiation, viz., diiodo-tyrosine and thyroxine. With the "growth" acids, we are not able to arrange such a continuous series from the simple amino acid molecule to the more complex molecule of the growth hormone. The chemistry of the growth hormone, or hormones, is as yet little understood and the physiological factors involving growth are not as evident as are those connected with differentiation, among which the thyroid secretion plays the chief rôle.

SUMMARY

(1) Experiments on tadpoles are described which show that some α-amino acids—phenyl-alanine, tyrosine, tryptophane—exert on differentiation an accelerating influence which in quality is comparable to that of diiodo-tyrosine (resp. thyroxine), though far less pronounced in quantitative effect.

(2) These acids are called "differentiation" acids, of which phenyl-alanine is the weakest, tryptophane usually the best.

(3) It was found that the "differentiation" acids support the action of diiodo-tyrosine. In some instances a mixture of tyrosine, or tryptophane, plus diiodo-tyrosine, influences differentiation almost as strikingly as diiodo-tyrosine alone, the absolute acid concentration being the same in each case.

(4) The chemical relationship between the "differentiation" acids and diiodo-tyrosine is pointed out. All are aromatic acids. It is further mentioned that the aliphatic α-amino acid, alanine, also gives slight indications of a differentiation factor.

(5) We have then a continuous series of differentiators, advancing in degree of intensity from phenyl-alanine (perhaps from alanine) over diiodo-tyrosine to the actual hormone, thyroxine. The intensity of effectiveness increases as soon as iodine is introduced into the molecule (viz., the step from tyrosine to diiodo-tyrosine), and with the number of I atoms introduced into the molecule (viz., the step from diiodo-tyrosine with 2 I to thyroxine with 4 I).

(6) If it is true that the amino acid precursors of the thyroid hormone carry in their structure a linkage which makes for differentiation, it is clear why iodized *proteins* are so effective in accelerating differentiation.

(7) It is also pointed out that another group of amino acids, arginine, lysine and cystine, facilitate growth. At present it is not yet possible to trace the chemical relationship, if any, between these "growth" acids and the "growth" hormone or hormones.

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ENDOCRINE GROWTH DEFICIENCIES: DIAGNOSIS AND TREATMENT

A PRELIMINARY CLINICAL REPORT

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DETROIT

Human beings physically handicapped by dwarfism have been stimulated to grow by the therapeutic application of the growth-producing hormone from the anterior lobe of the pituitary gland.*

This preliminary report presents seven cases of growth deficiency in which extrinsic factors were eliminated by a diagnostic survey. The growth deficiency had existed for varying periods of time, and in all cases there was a control period of observation in which there was no growth. A classification of growth deficiency is presented. The development of a specific growth hormone is outlined and the methods and results of its application in a series of cases is described.

The pituitary growth hormone is believed to be the controlling factor in general somatic growth. By somatic growth is meant growth which involves every body structure, including the individual cell. This growth hormone is manufactured in the anterior lobe of the pituitary gland and is apparently gland specific since it has not been derived from any other source. The cytological source is the eosinophilic cell. Evans and Long (1), in 1921, first recognized and demonstrated this hormone. Their first preparation was a saline suspension of finely ground anterior beef pituitaries which, when injected intraperitoneally into rats daily for several weeks, produced animals twice the size of the untreated controls. Improvements in preparation were extraction with dilute alkali, neutralization, centrifugation, and sterilization. Putnam, Teel and Benedict (2) in collaboration with Bugbee, Simond and Grimes (3), salted out the protein fraction and demonstrated that the growth principle is contained therein. A practical preparation was prepared by the latter workers by dissolving the protein precipitate in 0.02N sodium hydroxide so that 2 cc. represented the extractives from 1 gram of fresh anterior lobe. They added butyl alcohol as a preservative. Under these conditions the extract retains its potency for months, at least if kept in the refrigerator. Evans (4) claims to have isolated this hormone in crystalline form and his evidence is awaited with interest.

Material and Methods. We have applied this new therapeutic agent in a group of carefully selected cases from our private practice. Before treat-

*The therapeutic agent used in this study was Antuitrin-G. This is a product not yet commercially available and was supplied to us by the Research Laboratory of Parke, Davis & Company for a preliminary research test. The letter "G" is used to differentiate the growth from the sex factor.

ment was instituted a complete diagnostic survey was made and all possible non-endocrine factors eliminated. This survey consisted of a comprehensive history, physical examination, laboratory examination, including routine blood count, urinalysis, Wassermann test, complete blood chemical analysis, basal metabolic rates and Roentgen ray studies of osseous development. Previous to the studies presented herein the only human subject reported to have received the growth hormone was treated by Engelbach (6), using Evans' extract, and showed a favorable growth response.

In the series of cases presented in this report the extract described by Bugbee, Simond and Grimes was used. This extract, when injected into normal animals, produced acromegaly. Its administration, too, produced normal growth in hypophysectomized animals as compared with control litter mates (5). Sterilization of the extract is obtained by filtration through germ-proof filters. It retains is potency if kept at a low temperature, but insufficient work has been done to prove whether such protection is absolutely essential.

Treatment: Preparation and Dosage. Treatment was started with an initial dose of 0.5 cc. of Antuitrin-G, subcutaneously, three to five times each week. This was rapidly increased in 0.5 cc. amounts until a total of 5 cc. per dose was given. It was our intention to give even larger doses, but because of the scarcity of the extract it was necessary to reduce the dose to 2 cc. From this preliminary investigation it seems that results may be obtained in the human with relatively smaller doses, in proportion to body weight, than were necessary in animal experimentation.

With the exception of a single instance no untoward reaction was noted. This reaction consisted of slight swelling and redness at the site of injection. The patients showing thyroid insufficiency were given desiccated thyroid gland orally to tolerance.

CASE HISTORIES

Case No. I. January 29, 1932. Male. Age, 13 years 6 months. Occupation, schoolboy.

Diagnosis: Hypopituitarism.

History: The mother gave a history of normal endocrine response during pregnancy which went to full term. The weight at birth is not known, but the patient's mother noted that he was not so long as the average baby and that he had always been shorter than other boys of his own age. His physical development continued to be retarded up to the time of treatment, but his mental progress was normal.

Family History: No endocrine abnormalities were noted.

Physical Examination:

	Actual	Normal Variations for Age
Weight	79.0 lbs.	79.3–100.3 lbs.
Height (Standing)	55.0 ins.	57.8– 61.8 ins.
Upper Measurement	25.5 ins.	28.2– 31.0 ins.
Lower Measurement	28.5 ins.	29.0– 31.8 ins.
Circumference of Head	21.2 ins.	21.5 ins. (Optimal)
Circumference of Chest	26.7 ins.	28.6 ins. (Optimal)
Circumference of Abdomen	23.7 ins.	25.0 ins. (Optimal)

The patient showed general structural underdevelopment with poorly developed musculature. There was no obesity. The upper teeth showed exaggerated spacing. The testicles showed some slight underdevelopment. There was beginning pubic hair growth but no axillary hair. The other findings were normal.

Laboratory Examinations: The results of the urinalysis, blood count, and blood chemical examinations were within the limits of normal. The blood Wassermann reaction was negative. The basal metabolic rate was zero and minus 5 per cent. Roentgen rays for osseous development were within the limits of normal. Roentgen ray examination of the thymic region and sella showed no abnormality.

Course: This patient was under observation for a period of four months before treatment was instituted and showed no growth. Three months after treatment was instituted the patient showed an increase in height from 55 inches to 56.5 inches.

Case No. II. April 1, 1932. Female. Age, 15 years. Occupation, student, private school.

Diagnosis: Hypothyropituitarism.

History: The patient was adopted at the age of 6 months and was a very small baby. At that time she had rickets and was given cod liver oil. She talked at 18 months, but did not walk until after two years of age. She was always slow in school. She is now under a private tutor and is doing quite well. Her maturity occurred between 11 and 12 years of age. Her periods were regular and normal.

Family History: Not known.

Physical Examination:

	Actual	Normal Variations for Age
Weight	103.2 lbs.	95.7–119.7 lbs.
Height (Standing)	58.7 ins.	60.4– 64.6 ins.
Span	59.0 ins.	60.7– 65.3 ins.
Upper Measurement	29.3 ins.	29.8– 32.6 ins.
Lower Measurement	29.4 ins.	29.9– 32.7 ins.
Circumference of Head	21.1 ins.	21.6 ins. (Optimal)
Circumference of Chest	29.1 ins.	29.6 ins. (Optimal)
Circumference of Abdomen	26.0 ins.	24.8 ins. (Optimal)

This patient showed moderate structural undergrowth. There was a slight but definite lower girdle obesity. Her skin was dry, with scaling over the outer aspects of the upper arms. Her teeth were small and misaligned. Her third molar teeth were absent, and there were no unerupted teeth demonstrated by the Roentgen ray examinations. Her secondary sex characteristics were well developed for her age. There was a good growth of pubic and axillary hair. Her hands and feet were quite small but the fingers were short.

Laboratory Examinations: The results of the urinalysis, blood count, and blood chemical examinations were within the limits of normal. The blood Wassermann reaction was negative. Roentgen ray studies of osseous conditions of the hip, wrist, elbow, and ankle showed a slightly advanced development. Roentgen ray examinations of the sella showed normal outlines.

Course: This patient was under observation for a period of two months before treatment was instituted and showed no growth. Treatment was instituted May 22, 1932, at which time her height was 58.7 inches. On September 10, 1932, her height was 59.7 inches. In a period of three and one-half months this patient showed an increase in height of one inch.

Case No. III. January 18, 1932. Male. Age, 11 years. Occupation, schoolboy.

Diagnosis: Hypothyropituitarism.

History: The patient is the only child and represents the only conception. The pregnancy was normal, and his weight at birth was 10 pounds, 1 ounce. Dentition, walking, and talking occurred at 12 months. Physical and mental development progressed satisfactorily up to the fifth year. Since then his physical development had been quite stationary.

Family History: His mother was tall and slender, and his father was tall. His mother's sister had an exophthalmic goiter.

Physical Examination:

	Actual	Normal Variations for Age
Weight	53.5 lbs.	63.0– 79.4 lbs.
Height (Standing)	47.5 ins.	53.3– 57.1 ins.
Span	46.0 ins.	53.5– 57.7 ins.
Upper Measurement	23.5 ins.	26.1– 28.7 ins.
Lower Measurement	23.2 ins.	26.3– 28.9 ins.
Circumference of Head	20.7 ins.	21.1 ins. (Optimal)
Circumference of Chest	24.0 ins.	26.1 ins. (Optimal)
Circumference of Abdomen	22.5 ins.	23.3 ins. (Optimal)

This patient was structurally underdeveloped. His skin was extremely dry, inelastic and thickened. Over the sternum and lower extremities were lesions from scratching. There was a marked alabaster color present. The nose was quite blunt, and there was a pot belly present. The mucous membranes were quite pale. The pulse was relatively slow. There was a slight hypertrophy of the penis.

Laboratory Examinations: The urinalysis showed no evidence of disease. The blood count showed red blood cells, 3,400,000. The hemoglobin was 80 per cent. The blood Wassermann reaction was negative. The results of the blood chemical examinations were within normal limits. Roentgen ray study of the osseous conditions of the knee, elbow, wrist, shoulder, hip, and ankle showed a delay in development of 3 to 5 years. In addition there was a generalized proliferative and degenerative process in most of the epiphyses and chondral margins, most marked in the knees. Roentgenograms of the thymus and sella showed normal outlines. An orthopedic examination was made by Dr. L. C. Wagner. He ascribed the undergrowth and epiphyseal changes to an endocrine cause.

Course: The patient was under observation for a period of three months before the institution of treatment, and during this time he showed no change in height. April 25, 1932, he was placed upon Antuitrin-G. The total height at that time was 47.5 inches. September 16, 1932, his total height was 50.2 inches. This shows an increase in height of 2.7 inches in a period of four and one-half months.

Case No. IV. April 2, 1932. Female. Age, 9 years 5 months. Occupation, school girl.

Diagnosis: (1) Hypothyropituitarism. (2) Enlarged thymus.

History: The mother had a severely toxic pregnancy. The patient's weight at birth was 8 pounds. Development during the first year was normal. During her second year it was noted that she was quite clumsy and fell frequently. She did not enter school until the age of 8 years. Up to that time her mother believed that she was mentally retarded. Following the administration of thyroid her mentality improved, but there was no noticeable increase in stature. In June, 1931, her height was 42.2 inches.

Family History: The father was tall and overdeveloped. One brother, two years of age, showed a marked structural overgrowth.

Physical Examination:

	Actual	Normal Variations for Age
Weight	54.2 lbs.	53.6– 67.2 lbs.
Height	42.7 ins.	50.1– 53.7 ins.
Span	43.0 ins.	49.6– 53.4 ins.
Upper Measurement	23.0 ins.	25.0– 27.4 ins.
Lower Measurement	19.7 ins.	24.6– 27.0 ins.
Circumference of Head	21.5 ins.	20.6 ins. (Optimal)
Circumference of Chest	24.0 ins.	24.6 ins. (Optimal)
Circumference of Abdomen	24.0 ins.	21.5 ins. (Optimal)

Structurally this patient showed moderate undergrowth and was short and stocky. Her skin was extremely dry and inelastic with some subdermal thickening and a generalized pallor of the alabaster type. Her scalp hair was fine but extremely dry. The eyelids were somewhat thickened. The nasal bridge was low and the lips were pouting. There were only two upper central incisors present. Her upper abdomen was quite prominent, and there was a small umbilical hernia.

Laboratory Examination: The results of the urinalysis, blood count, and blood chemical examinations were within normal limits. The blood Wassermann reaction was negative. Roentgen study of the osseous development of the wrist, elbow, ankle, knee, and hip showed a delay of 3 to 4 years with the same chondroepiphysitis present in Case No. III. Roentgen rays of the thymus showed an enlarged thymic shadow.

Course: This patient was under observation from April 2, 1932, to May 25, 1932, before treatment was instituted and showed no growth. At this time the patient's total height was 42.7 inches. September 10, 1932, the patient's height was 44.2 inches. A total increase of 1.5 inches in height resulted in a period of three and one-half months.

Case No. V. November 27, 1931. Male. Age, 18 years 6 months. Occupation, student.

Diagnosis: Hypopituitarothyroidism.

History: The patient's birth weight was 7½ pounds. His growth and mental development were normal during the first and second years. Beginning at the third year his mother noted that he was smaller than other babies of his age, and that growth retardation had continued since that time. During the past year, under the observation of a physician, it was determined that he had grown one inch. His progress through school was satisfactory during his first three grades but since then he had difficulty. He was eighteen years of age and had not graduated from high school. He was somewhat incorrigible, but his mother believed that this was due to his introspection because of his retardation in physical development.

Family History: No endocrine abnormalities were noted.

Physical Examination:

	Actual	Normal Variations for Age
Weight	100.0 lbs.	113.3–142.3 lbs.
Height (Standing)	52.5 ins.	64.9– 69.3 ins.
Span	50.0 ins.	66.6– 71.8 ins.
Upper Measurement	28.5 ins.	31.3– 34.3 ins.
Lower Measurement	25.0 ins.	32.2– 35.2 ins.
Circumference of Head	21.0 ins.	22.4 ins. (Optimal)
Circumference of Chest	29.5 ins.	34.1 ins. (Optimal)
Circumference of Abdomen	29.7 ins.	28.4 ins. (Optimal)

This patient was short in stature but stocky. His head was slightly large compared with the rest of his body. His external genitalia were well developed. There was no axillary or pubic hairgrowth. His nose had a low bridge and his lips were thickened and pouting. His hands and feet were relatively small, and his skin was dry and scaly.

Laboratory Examination: The results of the urinalysis, blood count, and blood chemical examinations were within normal limits. The basal metabolic rates were minus 20, minus 24, and minus 15 per cent. The electrocardiograph showed slight right axis deviation. Roentgen study of osseous development of the wrist, elbow, knee, and ankle showed a delay in development of two to four years. Roentgenograms of the thymus and sella showed normal outlines.

Course: The patient was under observation for a period of five months before treatment was instituted. During this time he showed an increase in growth of one-half inch. On April 23, 1932, he was placed on Antuitrin-G. At that time his height was 53.0 inches. Measurements taken on September 21, 1932, showed his height to be 55.7 inches. This shows a total increase in height during a period of five months of 2.7 inches.

Case No. VI. March 29, 1932. Male. Age, 14 years 7 months. Occupation, student, private school.

Diagnosis: Hypopituitarothyroidism.

History: His mother gained about 30 pounds during this pregnancy. The patient walked and talked at two years. At the age of 14, six of his deciduous teeth had to be removed. These should have been lost at the age of 6 or 7. Until the age of 5 he was considered normal in growth. He had numerous infections after this age. When first seen by his physician, two years ago, he had a basal metabolic rate of minus 20 per cent. He was then given thyroid and since that time had grown from 48.7 to 52.0 inches. There was no mental retardation.

Family History: On the paternal side of the family there was a tendency to overgrowth; and on the maternal side, to undergrowth, but there were no giants nor dwarfs.

Physical Examination:

	Actual	Normal Variations for Age
Weight	55.0 lbs.	85.0–108.0 lbs.
Height (Standing)	52.0 ins.	59.5– 63.7 ins.
Span	52.0 ins.	60.7– 63.3 ins.
Upper Measurement	24.0 ins.	28.8– 31.8 ins.
Lower Measurement	28.0 ins.	29.7– 32.7 ins.
Circumference of Head	20.0 ins.	21.7 ins. (Optimal)
Circumference of Chest	23.2 ins.	29.7 ins. (Optimal)
Circumference of Abdomen	21.0 ins.	25.9 ins. (Optimal)

There was a marked structural underdevelopment. The patient was not obese. His skin was dry with a slight subdermal thickening. His eyebrows were scanty, and there was no axillary or pubic hair. There was a relative hypoplasia of the external genitalia.

Laboratory Examination: The results of the urinalysis, blood count, and blood chemical examinations were within normal limits. The basal metabolic rates were minus 10 and minus 8 per cent. Roentgen ray study of osseous development of the ankle, elbow, and hip showed a delay of 1 to 3 years. Roentgen examination of the thymic area and sella showed normal outlines.

Course: This patient was under observation for two months, from March 29, 1932, to June 1, 1932, without treatment, and showed a stationary growth. At this time his total height was 52 inches. This shows an increase of 2.7 inches in a period of three and one-half months.

Case No. VII. November 24, 1931. Female. Age, 7 years 4 months. Occupation, school girl.

Diagnosis: Hypopituitarism.

History: The patient was one of two children. She had one sister two years nine months old who was one inch less in height than the patient. Her mother's pregnancy and labor were normal. The patient's weight at birth was 6½ pounds. She was considered a small baby but not abnormally so until she was about one year of age. Dentition occurred at eleven months, but she did not walk until twenty-two months old. She talked the first year. She has always been subject to colds. As stated, she was about the same size as her three-year-old sister. No actual measurements or weights were ever taken. Her mentality tended towards precocity.

Family History: No immediate endocrine abnormalities were noted, but on the paternal side the father's sister also had a very much retarded growth. She was of adult age and only 4 feet in height. Her weight was probably less than 100 pounds. Her genital function, however, was evidently normal for she married and had three sons.

Physical Examination:

	Actual	Normal Variations for Age
Weight	30.7 lbs.	42.1– 52.3 lbs.
Height (Standing)	36.7 ins.	45.2– 48.4 ins.
Span	37.0 ins.	44.3– 47.7 ins.
Upper Measurement	18.7 ins.	23.4– 25.4 ins.
Lower Measurement	18.0 ins.	21.6– 23.6 ins. (Optimal)
Circumference of Head	18.5 ins.	20.3 ins. (Optimal)
Circumference of Chest	19.5 ins.	22.7 ins. (Optimal)
Circumference of Abdomen	19.0 ins.	20.5 ins. (Optimal)

Figure 1. Comparison of Case VII (right) at the age of 6 years with her normal sister at the age of 1½ years. All cases presented showed a similar structural undergrowth in varying degrees.

This patient showed marked structural undergrowth with miniature though proportionate stature throughout. Her features had perfect placement. Her teeth were normally developed for her age. A temperature of 99 to 100 was noted several times. As no infectious origin could be found it was ascribed to an endocrine hypoactivity. It subsided during treatment and remained normal.

Laboratory Examination: The results of the urinalysis, blood count, and blood chemical examinations were within normal limits. The blood Wassermann reaction was negative. The basal metabolic rate was minus 7 per cent. Roentgen ray study of osseous development of the wrist, hip, and ankle showed a delay in development of 1 to 3 years. Skiagrams of the thymic area showed a persistent thymic shadow; those of the sella and the chest showed no evidence of disease.

Course: The patient was under observation for a period of six months, from November 24, 1931, to June 1, 1932, without treatment. On this last date her total height was 36.7 inches. June 1, 1932, she was placed upon treatment, and measurements taken on September 6, 1932, showed a total height of 38.5 inches. This shows an increase in height of 1.8 inches in a period of three months.

DISCUSSION

Seven cases of endocrine growth deficiency all presenting varying degrees of dwarfism were treated with Antuitrin-G. All showed a favorable response. That this response was due to specific therapy is evident from the fact that all patients were under observation for a period of two to six months before treatment was started, and none, with the exception of Case V, showed growth during the control period. The duration of specific treatment with the growth hormone was from three to five months. Their statural growth was increased from one to two and seven-tenths inches. Case V showed a growth of 0.5 inches in five months under thyroid therapy. When placed on Antuitrin-G he grew 2.7 inches in five months.

TABLE I

Endocrine Growth Development
Favorable Response

Case No.	Sex	Age		Actual Height	Normal Variations		Length of Control Period Month	Change in Height During Control Period	Osseous Development	Type of Deficiency	After Treatment			
		Yr.	Mo.	Inches	Min. Inches	Max. Inches					Duration of Treatment Month	Height Inches	Gain in Height Inches	Remarks
1	M	13	6	55.0	57.8	61.8	4	None	Normal	—P	3	56.5	1.5	B.M.R., ±0%
2	F	15		58.7	60.4	64.6	2	None	Slight advance	—TP	3½	59.7	1.0	B.M.R., —12%
3	M	11		47.5	53.3	57.1	3	None	Delay 4 years	—TP	4½	50.2	2.7	No B.M.R. Marked subjective improvement. Ohondro-epiphysitis.
4	F	9	5	42.7	50.1	53.7	2	None	Delay 3 years	—TP	3½	44.2	1.5	Marked subjective improvement. Chondro-epiphysitis. Enlarged thymus.
5	M	18	6	52.5	64.9	69.3	5	Gain of .5 in.	Delay 3 years	—PT	5	55.7	2.7	B.M.R., —20%
6	M	14	7	52.0	59.5	63.7	2	None	Delay 2 years	—PT	3½	54.7	2.7	B.M.R., —10%. Mentality improved.
7	F	7	4	36.7	45.2	48.4	6	None	Delay 1 year	—P	3	38.5	1.8	B.M.R., —7%

—P denotes hypopituitarism.
—TP denotes hypothyropituitarism.
—PT denotes hypopituitarothyroidism.

Case IV was under thyroid therapy without growth before she was referred to us. Case VI, under thyroid therapy, grew 3.3 inches in two years. This is contrasted with his growth of 2.7 inches in three and one-half months of treatment with Antuitrin-G. These cases offer evidence that the growth obtained in our series was due to the Antuitrin-G and not to the thyroid therapy.

Classification and Symptomatology of Endocrine Growth Deficiencies. The development of the "pituitary growth hormone" and its clinical application suggests a group of disorders which may be appropriately termed "Endocrine Growth Deficiencies." The following classification of endocrine growth deficiencies is suggested:

I. Aneoplastic (Functional)
   1. Hypopituitarism (anterior lobe deficiency).
   2. Hypopituitarothyroidism (primary anterior lobe and secondary thyroid deficiency).
   3. Hypothyropituitarism (primary thyroid and secondary anterior lobe deficiency).

II. Neoplastic (intrasellar and extrasellar tumors).

III. Hypergenitalism, parathyroidism, and suprarenalism.

The Aneoplastic Variety. By functional growth deficiency is implied a hyposecretory state of the eosinophilic cell of the anterior lobe of the hypophysis. It naturally follows that there is an underproduction of the growth hormone. The opposite of this condition is seen in pituitary gigantism or acromegaly accompanying adenomatous eosinophilism. In this hyperfunctional state there is an increase in the number of the cells and probably a hyperactivity of the individual eosinophilic cell with an excessive secretion of growth hormone. Functional growth deficiencies may be divided into uniglandular or pluriglandular types. It is fairly well recognized that there is an inherent interdependence and interaction in the endocrine chain, especially between the pituitary and the thyroid. Hypopituitarism as such is not common nor, on the other hand, is it rare. The rarity of of its recognition, no doubt, has been due to a previous lack of diagnostic acumen. The biglandularisms, the hypopituitarothyroidisms and the hypothyropituitarisms are much more common.

The Neoplastic Type of growth deficiency is exceedingly rare and includes both the extrasellar and intrasellar tumors. The diminution in secretion of the growth hormone in this variety doubtless is the result of eosinophilic cell atrophy caused by direct pressure.

The influence of the other endocrine glands upon growth is not so well understood, but they do have an apparent influence. In hypergenitalism before the normal time for adolescence we see, associated with the hypertrophy of the external genitalia, a period of rapid somatic growth, which soon ceases; probably because of an excessive production of the sex hormone. At the completion of sex maturity we normally see a closure of

the various epiphyseal centers. Increase in length of the long bones then is retarded. This same condition is brought about in hypergenitalism and the early rapid growth then ceases entirely. Parathyroidism and its relationship to calcium metabolism is admitted as a factor in growth and development, especially of the osseous system. The subject is too broad to be discussed further in this paper.

Diagnosis. In the diagnosis of functional growth deficiencies two objective criteria are stressed, statural measurements and roentgenographic studies of the osseous centers. The first and more important one is measurement. Within the infantile and juvenile periods the eosinophilic cells are histologically more abundant. Evidence that they are functionally more active is shown by the clinical observation that one-half of the total growth in the human is attained during the first three years of life. It therefore follows that the earlier the diagnosis is made, and the growth hormone given, the better will be the ultimate results. The measurements in all growth deficiencies will obviously fall below the minimal normal measurement.

The second diagnostic means is the Roentgen study of the osseous development which is of greatest value in the pluriglandularisms—thyropituitarism and pituitarothyroidism. From our experience in the uniglandular or uncomplicated hypopituitary growth deficiency, we can state that the time of appearance and development of the various centers of ossification is normal or may be slightly precocious. Owing to a general somatic undergrowth, however, the skeletal structures will show a diminution in size when compared with that of the normal.

The x-ray evidence of retardation of osseous development is conclusive of the subthyroid factor. There are additional subjective and objective findings readily obtained which help to differentiate the pituitary from the thyroid as the primary gland at fault. In pituitarothyroidism the bone photography is diagnostic only after the infantile period. The course during the prenatal period of osteophytic changes in the joints, blunting of the peak bones, coarseness of the features and the development of chloasma or vitiligo in the mother and the birth of an undersized baby, suggests a primary hypopituitarism. The developmental history of this child during the infantile period shows no delay in dentition, walking or talking. Mentality is unimpaired, and as stated above, the Roentgen ray shows very little skeletal abnormality. Accurate physical measurement is the most important physical sign for making the diagnosis. If this infant with measurements below the minimal normal is untreated, the onset of juvenility will usually reveal a secondary subthyroidism which can be determined by the delay in osseous development by Roentgen examination. Furthermore, if the insufficiency of the thyroid becomes great enough, mental retardation, low basal metabolic rate and other well-known signs will be superimposed upon the growth defect.

In primary subthyroidism the x-ray findings are pathognomonic at birth or even late in utero. Retardation of osseous development at birth, which is determinable by roentgenograms of the knee and ankle, predicates subthyroidism. The additional differential signs are contrasted to those of the infant born exhibiting a primary hypopituitarism. In primary hypothyroidism a mother giving a history during pregnancy of an abnormal increase in weight, dermal changes, mental retardation, pallor, slow pulse and diminished metabolic rate will usually give birth to an infant which is overweight. In the developmental history of a subthyroidism there is a delay in walking, talking, dentition and mentality. Growth and weight at birth are usually above normal and continue so before the juvenile period. It is at this time that the associated pituitarism is manifested and structural undergrowth becomes manifest. It is not until early juvenility that the associated hypothyroidism occurs in the hypopituitarothyroidism.

Roentgen evidence in the neoplastic types when present includes in addition to the findings heretofore described changes in the sella turcica, usually erosion or enlargement.

Cases I and VII, with uniglandular involvement, were diagnosed as hypopituitarism. Cases V and VI, with biglandular involvement, were diagnosed as hypopituitarothyroidism, implying a pituitary insufficiency at birth followed by a secondary juvenile subthyroidism. Cases II, III and IV, with biglandular involvement, were diagnosed as hypothyropituitarism, showing a subthyroidism at birth and a later juvenile pituitary insufficiency. From the symptomatology presented in this report it is evident that Cases I and VII presented a uniform undergrowth throughout from birth without any following thyroid involvement. Cases V and VI, the hypopituitarothyroidisms, did not show subthyroid findings until after the onset of the juvenile period. In contrast, Cases II, III and IV presented subthyroid findings, delay in osseous development, late dentition, mental

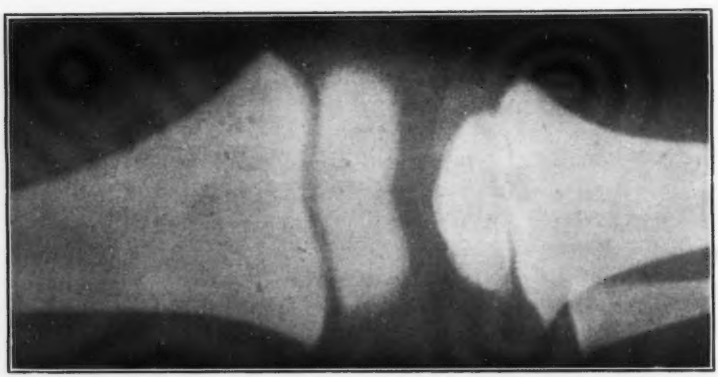

Figure 2. Case III. The osseous centers throughout show this abnormal appearance with normal roentgen appearance of the shafts.

retardation, et cetera, from birth with a later juvenile structural undergrowth.

In addition to the endocrine involvements Case IV showed a persistency of the thymus. It is not believed that the thymic factor is causal but rather expresses a lack of general involutionary change.

Cases III and IV of hypothyropituitarism presented a significant roentgenographic study. The osseous centers throughout showed a moth-eaten, fuzzy, ragged and poorly outlined appearance, together with a decreased density. The shafts show normal bone detail. At the present time roentgenologists and orthopedists term this a generalized chondro-epiphysitis with no suggestive etiology or therapy. These findings are in contradistinction to those in experimental acromegaly in which there is a generalized increased bone density of the osseous centers with osteophytic overgrowth. It would seem from these two observations that this condition of so-called chondro-epiphysitis is not necessarily inflammatory in character but may be due, in some cases at least, to the effect of the endocrine imbalance.

Three cases not reported in detail are included here because of the interesting relation between the growth and sex hormones which they indicate. Case A was a male, aged 32 years, with a standing height of 57.5 inches. Roentgen examinations showed non-union of his epiphyseal sutures, a delay of ten to twelve years. He had normally developed external genitalia, axillary and pubic hair, and was normally potent before treatment. Treatment produced an almost complete loss of libido.

Case B was a female, aged 15 years, with a standing height of 60 inches. There was normal epiphyseal closure. She had normal sexual development, maturing at twelve and one-half years of age with normal rhythmicity of menstrual periods. During the course of her treatment she experienced two periods of amenorrhea.

These two cases indicate that the growth hormone is antagonistic to the sex hormone.

Because of the degree of sex maturity and function in Cases A and B, an unfavorable prognosis was indicated. When sexual maturity is completed, ninety per cent of the total growth has been attained. At this time the eosinophilic cells are relatively fewer, and consequently less growth hormone is elaborated. The other cellular elements of the anterior lobe, the basophile and the chromophobe, then appear in greater numbers with a consequent production of more sex hormone. Either directly or through an interdependent reaction, sexual maturity normally brings on a closure of the epiphyseal sutures with a cessation of growth. The opposite condition, increased growth with open epiphyses, is seen in eunuchoidal gigantism.

The unfavorable prognosis was supported by the results of treatment. Case A was under treatment for four months and showed an increase in

height of only 0.5 inches. Case B was under treatment for four months and showed an increase in height of only 0.2 inches.

The small amount of growth obtained in Case II was attributed to the degree of sexual maturity which she had attained.

Case C, who was examined but not treated, was a male, aged 20 years, with a standing height of 52.5 inches. Roentgen examination showed a delay in epiphyseal closure of four to five years. His genitalia were puerile and he had no axillary nor pubic hair. Because of his lack of sexual development a favorable prognosis was made in contrast to Cases A and B.

SUMMARY

I. Seven human subjects with endocrine growth deficiencies in which the growth hormone was indicated and administered showed a definite growth response.

II. A group of endocrine disorders termed "Endocrine Growth Deficiencies" is submitted with a classification.

III. Outstanding diagnostic signs for the various types under this classification are described.

IV. This report indicates that the growth hormone is a specific growth stimulant in the human being.

V. A plea is made for the early recognition and treatment of these disorders which will materially improve their prognoses.

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DISEASES OF THE SUPRARENAL GLANDS*

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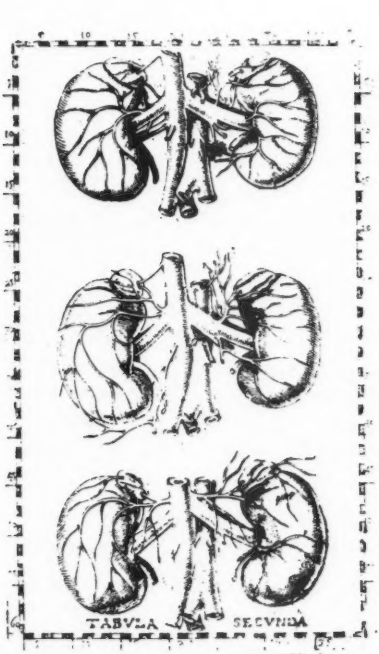
The immediate results of the treatment of patients with Addison's disease with the suprarenal cortical hormone of Swingle and Pfiffner, have been so striking as to suggest the desirability of reconsidering the whole field of the suprarenal glands and their diseases. What has been learned from the use of this new, active principle may help to throw some light on the nature and function of the suprarenal glands in health and in various diseases.

The suprarenal glands were first described by Eustachius in 1563 (Fig. 1), but it was not until Addison's classical study that anything was known



STRVCTVRA. 39

De glandulis quæ renibus incumbunt. Cap. VI.

QVANQVAM hæc, quæ de renum ſuperficie diximus, ſatis multa uideri poſſint: nihilominus ne aliquid in hac tractatione prætermiſſum eſſe quiſpiã mihi iure obijciat: conſentaneum eſſe duxi de quibuſdam renum glandulis ab alijs Anatomicis negligenter prætermiſſis hoc loco ſcribere. Nam utriq; reni, in eminentiori ipſorum regione, quæ uenam cauam ſpectat, glandula adhæret. hæc autem externæ eorundem membranæ, quæ peritonæo tranſuerſi ſepti continua eſt, adeo adnectitur, ut non raro, niſi quis animum diligenter aduertat, euulſis renibus ipſam ſepto tranſuerſo ſtrenue adhærentem quaſi nulla ſit, prætereat. Eius ſubſtantia quemadmodum & figura renibus fere reſpõdet: licet ſæpe depreſſa quoque ac adeo lata occurrat; ut potius placentæ, quàm renis formam referre uideatur. longitudinem habet duorum digitorum: latitudinem unius; craſſitudinem mediocrem ſortita eſt. quæ omnia pro ratione ſuæ figuræ, quum ea una ſemper non ſit, non minimum quoque uariare cernuntur. magnitudinem præterea utraque harum glandularum nec parem obtinet, nec perpetuo ſeruat: ſed uiciſſim nunc hæc, nunc illa eſt maior altera: quemadmodum item renis cui quæuis earum inſidet, altero maior uiciſſim eſt. euenit tamen frequentius, ut dextra, ſicut etiam renis, ſiniſtram ſuperet. hoc glandularum genus deſideraſſem a prioribus Anatomicis, & ab his, qui hodie hanc artem excolunt, quique admodum prolixam humanarum partium

Figure 1. The first description of the suprarenal glands by Eustachuis, 1563.

*Read before the Association for the Study of Internal Secretions, Philadelphia, Pennsylvania, June 8 to 9, 1931.

of their function. Despite the fact that it has been more than three-quarters of a century since Addison proved that disease of the suprarenal glands was responsible for the clinical syndrome which bears his name, and despite the fact that other diseases of the suprarenal glands have been recognized clinically and pathologically, little is actually known of the specific functions of these tiny glands which are so necessary to life.

The suprarenal gland consists of two portions which are of different embryonic origin and apparently have distinct physiologic functions. The medulla of the gland is made up largely of chromaphil cells which are derived from the embryonic sympathetic system. Extirpation experiments show that it is not essential to life. The cortex is composed of epithelial cells arising from the wolffian body; the latter portion of the gland apparently is essential to life, as shown by the experiments of Biedl (13), Wheeler and Vincent, Houssay and Lewis, Crowe and Wislocki, and others.

Many hypotheses have been advanced in regard to possible functions of the suprarenal glands and their relation to those of the other endocrine glands, but these hypotheses, for the most part, rest on dubious ground and may be accepted only with reservations. It is known that the function of the cortex in some way concerns the growth of certain tissues, and the organs of reproduction, and is concerned with intake of food and its assimilation and with transformation of energy. Recent experimental work tends to emphasize the significance of the relation of the suprarenal cortex to the sex glands. The medulla is concerned largely with epinephrine, which stimulates the sympathetic nervous system and causes marked vasoconstriction.

Knowing that the two parts of the suprarenal gland differ morphologically, investigators long have attempted to isolate separate hormones from the cortex and the medulla. The active principle, epinephrine, was first isolated from the medullary portion by Abel and by Takamine. Cannon suggested that epinephrine furnishes an emergency stimulant and that increased amounts are discharged into the circulation when the gland receives a stimulus as the result of fear, rage, hunger and so forth. Pharmacologically, its action results in changes similar to those observed following stimulation of the sympathetic system. Therapeutically, it has proved of great value whenever stimulation of the sympathetic system is indicated.

Szent-Györgyi recently isolated hexuronic acid, an isomer of glycuronic acid, from the suprarenal cortex. It is concerned with phenol color reactions in vitro and perhaps in vivo. The pigmentation in Addison's disease seems in some way to be connected with this isomer. He found, on the other hand, that hexuronic acid did not prolong the life of suprarenalectomized dogs, and seemingly small amounts of it were without distinct therapeutic effect in two cases of Addison's disease in which we tried it. More recently studies by Szent-Györgyi indicate that hexuronic acid is identical with vitamin C and possesses marked antiscorbutic properties.

Numerous investigators have attempted for many years to isolate a cortical hormone for the treatment of Addison's disease. Among these are Rogoff and Stewart (54), Hartman and his collaborators (23, 24), Koehler, and Swingle and Pfiffner. Increase in the time of survival of animals following bilateral suprarenalectomy had been set up as the criterion of potency of these preparations. Rogoff and Stewart (54) reported prolongation of life of suprarenalectomized cats from the usual ten or eleven days to thirty-two days, and Hartman (25) and his collaborators reported survival for twenty-seven days. Rogoff and Stewart (53) also reported definite beneficial results from the clinical use of their preparation in a small series of cases of Addison's disease. The preparation of an aqueous extract of the suprarenal cortex, capable of keeping suprarenalectomized cats alive indefinitely, was first announced by Swingle and Pfiffner (58) in March, 1930. Subsequently, they reported that by administration of this extract they were able to revive comatose animals that were prostrate and on the verge of death from suprerenal insufficiency, and also to restore them to an apparently normal condition and to keep them in a semblance of perfect health by daily injections.

It is hoped that experimental and clinical investigations with the active cortical extract, with epinephrine, and with hexuronic acid may help to penetrate the haze of ignorance in which the whole subject is shrouded, and to reveal clearly the real function of the suprarenal cortex. Our clinical studies so far have taught us that the hormone elaborated by the cortex of the suprarenal gland has a profound effect on metabolism. The stimulation of hunger, the reëstablishment of normal gastro-intestinal function, the great increase in weight, in energy, and in strength, especially of the muscles, and the decolorizing of the skin, are most striking and impressive, following administration of the cortical hormone to patients suffering from Addison's disease. On the other hand, it has evidenced no unusual effect on sex or on blood pressure.

RELATION OF THE SUPRARENAL GLAND TO OTHER GLANDS OF INTERNAL SECRETION

All of the endocrine glands seem to be concerned, in one way or another, with nutrition, growth, and reproduction. The exact influence of each specific hormone is little understood at present. Perhaps, when the function of any one gland is upset, there is a related disturbance in other hormone-producing glands. It is sometimes extremely difficult in a given case to be sure of what constitutes the primary disturbance. Even in cases in which the clinical data seem to point to a definite lesion in some one gland, the pathologic data may indicate complex disturbances involving other glands as well.

In diseases of the suprarenal glands, there is sometimes concomitant dysfunction of the gonads, thyroid gland, pituitary body or pancreas. The basis for the related functional disturbances in other glands is not entirely

clear. In cases of cortical suprarenal tumor, both in children and in adults, it simultaneously enhances the activity of the sex hormone, although there is no evidence that it affects spermatogenesis. This results in the development of secondary sexual characteristics of the male type. It seems that excessive secretion of the cortical hormone exerts an inhibitory influence on ovarian secretion in adults, although it may stimulate menses in girls before puberty. Why or how these changes are indicated is not known.

Some writers, notably Marine (40, 41), have claimed that the suprarenal gland is involved extensively in cases of exophthalmic goiter. In this connection it may be noted that incomplete preliminary studies with the cortical hormone of patients with exophthalmic goiter make us feel that the suggestion of Marine as to the participation of the suprarenal gland in hyperthyroidism is deserving of thorough investigation. On the other hand, Guttman found in his pathologic study of the cases of Addison's disease reported in the literature, that evidence of disturbance in the thyroid gland which could be regarded as being of any significance was not discernible pathologically. Yet the basal metabolic rate of patients with Addison's disease is usually low, and under treatment with the cortical hormone tends toward a normal level. Another fact which may be of interest in this connection is that one of our patients with Addison's disease, who did not respond to treatment with a large amount of the cortical hormone, had an extremely low basal metabolic rate, —30 per cent, and necropsy revealed very marked atrophy of the thyroid gland. Whether this was a factor in her resistance to specific organotherapy, of course, is not known.

In disease of the suprarenal glands there are evidences sometimes of associated changes in the pituitary gland. Again, tumors of the pituitary gland are sometimes associated with changes in the suprarenal gland, together with clinical evidences of suprarenal dysfunction.

In some cases of suprarenal tumor there is disturbance of metabolism of sugar. Usually, hyperglycemia is observed, but one case has been reported by Anderson in which there were evidences of hyperinsulinemia.

Not enough is known of the various hormones secreted by each gland, and of their functions to permit clear understanding of the interrelation of function of various glands in health and disease, certainly not enough to justify the employment of fixed mixtures of hormone. With an unlimited supply of the cortical hormone, further clinical and physiologic studies should be made, in an effort to untangle the multiple details of this interrelationship of function of the various glands of internal secretion.

CLASSIFICATION OF DISEASES OF THE SUPRARENAL GLANDS

In general, excessive activity of either the cortex or the medullary portion of the suprarenal gland is due to some type of tumor, whereas hypofunction is due to atrophy or some disease destructive to tissue, such as tuberculosis. Since the suprarenal gland is composed of two parts, dif-

fering distinctly both functionally and morphologically, and since the function of these glands is so complex, it is to be expected that there is a large variety of clinical syndromes due to diseases of these glands. The clinical picture in each case depends on whether there is hypofunction or overactivity, on the age of onset of the disease, and on the extent and nature of the disease of the cortex or medulla, one or both.

The diseases which result from hyperfunction of the cortical part of the suprarenal gland are pseudohermaphroditism, pubertas praecox, virilism, and hirsutism. Medullary tumors are of three types: neuroblastomas, usually characterized by metastasis to the bones or to the liver; ganglioneuromas, which are benign and paragangliomas, which produce paroxysmal hypertension, or permanent hypertension. Hypofunction of the suprarenal glands as a whole results in Addison's disease. There is another clinical state which has been called, not without question, suprarenal insufficiency or hypoadrenia, and is supposed to be due to insufficient secretion of epinephrine.

Diseases of the suprarenal gland can be classified as follows:

Hyperfunction.

Cortical ("syndrome genitosurrenale"), gives rise to:

1. Congenital pseudohermaphroditism.
2. Infantile pubertas praecox.
3. Adult virilism and hirsutism.

Medullary, may be associated with:

1. Neuroblastoma with multiple marked metastasis to liver and bone.
2. Benign ganglioneuroma.
3. Paraganglioma with intermittent paroxysmal hypertension or permanent hypertension.

Hypofunction.

Suprarenal insufficiency [hypoadrenalism, hypoadrenia (?)]
Addison's disease.

CLINICAL MANIFESTATIONS OF HYPERFUNCTION

Cortical hyperfunction. Tumors arising from the cells of the suprarenal cortex resemble more or less normal cortical tissue. These may be simple, the results of hyperplasia, they may be adenoma with or without degeneration, or true carcinoma or hypernephroma (Jaffe).

Numerous cases of tumor of the suprarenal cortex have been reported in the literature. Tumors arising in this region have been associated with marked changes in bodily development and nutrition, and anomalous sex manifestations have been particularly striking. These changes include precocity, with or without change in sexual character, pseudohermaphroditism in children and adults, and virilism or hirsutism in adults. The

degree of functional response to suprarenal tumors of cortical origin depends mainly on two factors, the type of the tumor and the time of its onset. Hyperplasia or benign tumor, due to slow growth and long duration, do not cause as rapid changes as are caused by malignant tumors. However, the result depends more largely on the factor of time of onset. If the influence of the cortical growth, with its excessive cortical function, is brought to bear on an undeveloped organism, its effect is much greater than after full development of the sexual characteristics. Hence, the most complete effect, pseudohermaphroditism, results if the cortical changes begin during prenatal life. This will not be considered further, inasmuch as the condition is familiar to all, and since no satisfactory method of treatment is known. If changes in the cortex begin in the infant, precocity will develop with or without change in the secondary sexual characteristics. Finally, in adult life, the morphology of the genitalia cannot be much influenced, but symptoms indicating the same type of change are developed as in hirsutism and virilism.

A large proportion of these cortical tumors have been found in females, and there is a fairly large series in children, most of whom are girls. However, recently Holl has reviewed reports of five cases in males and has reported two cases from his own practice in male adults. As a rule the "maleness" is increased, but in one of these there was a marked trend toward feminism which developed in a man who was past forty years of age. The change consisted of hypertrophy of the mammary gland, atrophy of testis and penis and loss of libido and potentia. This was partially relieved by removal of a suprarenal tumor. In children there has been sexual precocity, which generally tends, even in females, toward the male type. Several instances have been reported of virilism developing in young girls before the age of puberty, with increased growth and male distribution of hair, hypertrophy of the clitoris, deepening voice, and masculine bodily conformation. In certain other cases in which cortical tumors have been found, there has been early female sexual development, with the onset of menstruation in early childhood. However, some authors claim that in cases of this sort, in which a suprarenal tumor has been found, there has been marked change either in the pituitary body or the ovary, which would account for the precocious menstruation. In any event, the interrelationship is important. A number of these cases of precocious sexual development in young girls has been seen in The Mayo Clinic, but in none of them was there sufficient clinical evidence to make a positive diagnosis of suprarenal dysfunction.

One of these patients (Fig. 2) was four years old when she was examined in the clinic. For nine months she had had an increased appetite and had gained rapidly in weight. About the same time her parents noticed that her voice was low-pitched and that hair had begun to appear in the axillae and pubic region. There had been no sign of menstruation. Examination showed her to be obese, with precocious secondary sexual characteristics. Abdominal masses could not

be palpated, and examination of the sella turcica and eyegrounds revealed nothing abnormal.

Within a few weeks of returning home the patient had an acute attack of nausea, vomiting, visual disturbance, headache and loss of consciousness. This was followed by a lethargic state which resembled that seen in patients convalescing from acute encephalitis. After this her condition improved, and then she had an attack of acute pyelitis which cleared up within a few days. After about two months she had a second attack, which was followed by marked cerebral disturbance. This affected her speech, and there were marked catatonic

Figure 2. Precocious sexual development of a girl aged four years. Clinical evidence was not sufficient to justify positive diagnosis of suprarenal dysfunction.

symptoms. Her blood pressure at that time was 76 systolic, and 30 diastolic, and there was a distinct left optic neuritis. The skull was not examined roentgenologically then, but previously, as has been recorded, such examination had given negative results. These symptoms had persisted for about two weeks when masses developed in both submaxillary and posterior cervical regions. About a week later there was a hemorrhage from one of these. There was a general increase in the very peculiar behavior and maniacal tendencies, and a few days after the hemorrhage the patient lapsed into coma and died several days later. Necropsy was not performed. Late cerebral symptoms suggest pituitary involvement—possibly a basophilic.

In the few cases of suprarenal cortical tumor in young boys that have been reported, there has been precocious sexual development, with enlargement of the external genital organs, changes in voice, and excessive growth of hair. Macera published a report of a case of this kind concerning a

boy aged thirty-four months, who six months before his death, had had an increasing growth of hair all over the body, but especially growth of the genitalia, which presented an adult appearance. There was gradual increase in the size of the abdomen and marked polydypsia. His disposition changed markedly; that is, he became more mischievous and more difficult to manage. The symptoms were initiated by a hard fall, and increased gradually. The polydipsia increased, but laboratory analysis failed to reveal any evidence of glycosuria. The patient died in a convulsion. Necropsy disclosed a large malignant tumor of the right suprarenal gland, with metastasis to the lungs and the liver. The pituitary body and other endocrine glands gave no evidence of disease.

In our files we find a similar record (Fig. 3), although necropsy was not possible.

Figure 3. Enlarged abdomen and precocious sexual development of a boy aged thirty months. A mass, palpated in the abdomen, was probably a suprarenal, cortical tumor.

A male child, aged thirty months, was admitted to the clinic in November, 1929, with the complaint that an abdominal mass had been present for one year, and a painful, swollen knee for one week. The patient was the only child of healthy parents and had developed normally in all respects until one year previously. At this time the mother had observed the abdomen to appear somewhat full, but as the child evidenced no complaint, a physician had not been consulted. A short time later, a few dark hairs had been seen growing in the axillae and coarse, black pubic hair had appeared. The abdomen had slowly enlarged, the

growth of pubic hair had become more profuse and the penis had increased in size. The voice had undergone a gradual but definite change, becoming low-pitched and masculine. Five months before the patient had been brought to the clinic, the family physician had palpated a tumor in the middle of the right side of the abdomen, and had suggested the diagnosis of suprarenal tumor. For one month before examination at the clinic, the child had complained of occasional pain in the right knee and one week before, definite swelling with redness had appeared in the knee.

On examination, the boy was seen to be well nourished, well developed, with the secondary sexual characteristics of an adult male. The voice was low-pitched and the facial features coarse, with thick lips. The penis and scrotum were of adult proportions, and there was a profuse growth of pubic hair. A hard, irregular tumor filled the entire righ side of the abdomen. There was also a hard swelling of the left thigh, which was thought to be caused by metastasis from the abdominal tumor. The hands and feet were small in proportion to the rest of the body. In view of the apparent extent of the malignant process, operation was deemed inadvisable and the child was given some roentgenologic treatments and was taken home, where he died a few months later.

In 1912, Glynn reviewed the cases of suprarenal hypernephroma in young women, associated with striking changes toward masculinity in sexual characteristics. Since then several cases of this type have been reported. In some instances the symptoms come on rather suddenly and progress rapidly; in others, the anomalous characteristics develop slowly and may last for many years without any great impairment in general health. It is assumed that in these latter cases the tumor grows slowly and is benign.

Perhaps the most interesting of all these cases is one reported by Holmes in 1925. The long period during which the patient was under observation before operation (two years) and after operation (nine years) makes this record especially valuable. A young woman had a large, slowly growing tumor of the cortex of the right suprarenal gland, associated with changes in the sexual organs (atrophy of the uterus, hypertrophy of the clitoris), disturbances of secondary sexual characteristics, with growth of hair, atrophy of the breasts, change in the distribution of fat, and a masculine muscular development of the arms and legs, accompanied by psychic changes. All of these symptoms disappeared within a relatively short time after removal of the tumor, and left the patient an apparently normal woman, which condition had continued for nine years following the operation at the time the case was reported.

More recently, Murray and Simpson reported recovery from virilism following removal of a suprarenal tumor from a woman aged thirty-six years. She had had amenorrhea for nine months before operation, and during this time an insatiable appetite had developed, with a consequent gain in weight. Following operation, menstrual function was restored, and her appetite and weight returned to their former natural state. An interesting feature of this case was the high blood pressures (200 and 120) and the increased pulse rate. After operation the pulse rate remained slightly above normal and the systolic blood pressure, although as a rule only about 120 mm. of mercury, was still very easily raised to 190 or 200 on slight excitement.

Feinblatt reported a record of a female physician, aged thirty-two years, who for seven months had amenorrhea, with increasing growth of hair on the body. She had severe constipation, with abdominal pain and distention. There was edema of the ankles and legs, with increasing brownish and iteric pigmentation. Emaciation and exhaustion were extreme, and the patient finally lapsed into coma and died. Necropsy revealed a tumor of the right suprarenal cortex and absence of the suprarenal gland on the left side.

Another classic example of the syndrome caused by tumor of the suprarenal cortex is to be found in the case reported by Lisser; that of a woman aged thirty-eight years. Fortunately, he obtained photographs of the patient before and after the onset of her illness. One such picture is worth pages of description. Dr. Lisser has abstracted her history as follows:

"The figure shows a normal appearing woman at the age of thirty-five years contrasted with her appearance three years later at thirty-eight. The extraordinary feature that at once attracts attention is the excessive hairiness of the face and thighs and the masculine pubic escutcheon, a characteristic heterosexual hypertrichosis. This rapid growth of hair on the face and body had begun a year and a half before these pictures were taken.

"The second noteworthy fact was abrupt cessation of menstruation eight months previously, whereas her periods had been regular and normal prior to that time. Examination of her genitalia showed a marked enlarged clitoris.

"She had lost 19 pounds in the previous seven months. Her basal metabolic rate was +17.2 per cent, which was not due to any clinical hyperthyroidism but probably associated with the malignant tumor of her right suprarenal cortex. She had had some bearing-down pains in the right lumbar region and an indefinite mass was felt behind the liver. Cholecystography showed a small, well outlined gallbladder, displaced inward and downward as if by a tumor in the right upper quadrant. Pyelogram of the right kidney showed it to be low as compared with the left, with rather large pelvis and appearance of pressure and flattening of the upper calyx.

"The combined evidence of virilism, and large clitoris, amenorrhea, and the localized evidence of tumor in the right upper quadrant left no question as to the diagnosis. Pelvic examination was negative and roentgenograms of the chest and skull showed no evidence of metastasis. In the hope that the tumor might be benign and removable, operation was performed, but a huge malignant mass was found which had already invaded the inferior vena cava. The patient soon died and an autopsy corroborated the diagnosis of malignant suprarenal cortical tumor."

The typical syndrome of hyperfunction of the suprarenal cortex was observed by Kennedy and Lister in a girl aged eighteen and a half years. There was a six-months' history of increasing obesity, with rapid increase in size of the external genitalia, but menstruation had not begun. There was a thick growth of hair over the back, and the pubic hair was much in excess of the normal for the patient's age. An irregular tumor the size of a fetal head was present in the left hypochondrium. This was removed at operation and proved to be a tumor of the left suprarenal cortex. The patient went into collapse and died thirty-six hours after the operation.

In the files of The Mayo Clinic we have the record of a case that was reported previously by Walters and Keyser, but we are abstracting it here, because we feel that it is of unusual interest.

A woman, aged thirty-seven years, the mother of ten children, was admitted to the clinic February 7, 1923, complaining of goiter, weakness, and skin trouble. Menstruation had occurred but once or twice between pregnancies, and since the last pregnancy, three years before, she had not menstruated. Two years before admission, the patient had noticed enlargement of the thyroid gland; since that time its size had increased but slightly. However, moderate nervousness, occasional tremor, intermittent attacks of precordial pain, and a jerking sensation in the heart had been noted. Intolerance for heat, perspiration, fatigue and dyspnea, with choking sensations, all brought out on moderate exertion, had been troublesome. Her appetite had increased, and she had gained 30 pounds (13.6 kgm.) in weight, but in spite of this she had lost strength and vigor. She complained of slight mental dullness. Eighteen months before admission, a blotchy erythema had appeared over the shoulders and chest. This acneform eruption had spread gradually over the entire body surface, with the exception of the hands and feet. Six months after the onset of the cutaneous lesion, the hair of the face, arms and chest had begun to increase in amount. This hirsuties had become so excessive that the patient had recently been forced to shave the face, and as the body hair had increased in amount, that of the scalp had become thin. For the last year before she came to the clinic, the patient had been troubled with a salty taste in her mouth, and six months before admission a form of stomatitis had developed. The quality of the voice had become increasingly coarse for more than a year. During this time she had also suffered from a dull, aching pain in the back, which was made worse by stooping or exercise. Twice in January, 1923, after severe exertion, she had expectorated a slight amount of bright blood.

At the time of examination, the patient weighed 130 pounds (59 kgm.) and was apparently well nourished. The skin was oily and blotchy. The thyroid gland was definitely enlarged, with a small, firm adenoma in the lower pole on the right side; aside from râles in the bronchi and roentgenologic evidence of old tuberculosis at the apex of the right lung, examination of the chest gave negative results. The abdomen was diffusely tender, and a smooth mass was palpable below the left costal margin, anteriorly. The urine contained a moderate amount of albumin, and sugar was present in the twenty-four-hour specimen in amounts varying from 5.9 to 6.5 gm. The concentration of sugar was from 111 to 143 mgm. in each 100 cc. of blood. The concentration of urea varied from 34 to 38 mgm. for each 100 cc. of blood. The blood pressure ranged from 124 systolic and 90 diastolic to 180 systolic and 110 diastolic. Roentgenograms gave evidence of a normal sella turcica. The basal metabolic rate varied from +15 to +28 per cent.

Exploration was made, February 28, 1923, and a tumor about 25 cm. in diameter, attached to the left kidney, was removed. The patient recovered well from the anesthesia, but within twenty-four hours elevation of pulse and temperature, and a low, indeterminable systolic blood pressure was noted. Epinephrine was given subcutaneously and by rectum, but on the fourth day she passed into coma, and died after several hours of unconsciousness.

At necropsy, hypoplasia of the right suprarenal gland, early hemorrhagic bronchopneumonia, terminal acute hepatitis and nephrosis were observed. A male habitus, acne, and hemorrhagic fat necrosis in the pancreas were also noted. The follicles of the thyroid gland were distended with colloid, and the epithelium was flattened. The pituitary and pineal bodies and the ovaries were normal.

The pathologic picture, both gross and microscopic, corresponded closely with that described by Glynn and others as characteristic of malignant suprarenal hypernephroma.

This case is of interest because enlargement of the thyroid gland, nervousness, tremor, tachycardia, hyperhydrosis, intolerance to heat, dyspnea, choking sensations, precordial distress, increased appetite, increased metabolic rate, and hypertension were associated with suprarenal carcinoma. The dyserasia of the skin, weakness, fatigue, alopecia, suppression of menstruation, change in voice, and increase in weight, all were suggestive of perverted function of the suprarenal cortex. This was determined from previous clinical evidence. The hyperglycemia and glycosuria are diffi-

cult to account for. Death following operation was of a type suggesting suprarenal insufficiency, and the small suprarenal gland found on the right side more or less confirmed such a view. Another of our cases is of great interest.

A woman, aged twenty-nine years, had become ill about a year before her examination at the clinic, when she had begun to gain weight and had had extensive acne, with disappearance of menstrual function. This had been accompanied by increased growth of hair of masculine distribution, tingling of the hands and feet, and loss of sexual desire. There had been a squeezing pain in the lower part of the abdomen, and she had noticed that she was more nervous and easily irritated than before. She gradually had become listless, and felt "dopey" much of the time. There had been bronzing of the face and neck and absence of sweating. She had become fatigued easily, but had had difficulty in sleeping.

At examination the patient appeared to be aged forty-five years rather than twenty-nine, and had a distinctly masculine appearance. There was acne of the face, chest and back; dirty, reddish brown pigmentation of the face and neck; and hypertrichosis of the face and body. The breasts were flat, and the skin seemed dry, thick and coarse. The anterior cervical glands were palpable, and the thyroid gland was slightly enlarged. There was some tenderness in the abdomen to the left of the umbilicus.

Laboratory findings were essentially normal, although there was some albuminuria, graded 1, and there was also a slight amount of pus in the urine. The Wassermann test of the blood was negative. The basal metabolic rate was —12 per cent. Roentgenograms of the sella turcica and of the thorax were negative. Chemical examination of the blood and tests of renal function gave normal findings.

Left suprarenalectomy was performed, following which the patient suffered from a postoperative psychosis. Histologic study of the gland revealed no pathologic change. She recovered from this completely, and was in good condition at the time of her dismissal. She returned six months later for reëxamination, seemed much improved, and reported that she was feeling very well except that she was easily fatigued. According to her physician's statement, within a year after the operation she felt and looked entirely normal. However, about that time psychopathic tendencies began to develop and she threatened to kill herself and her child. She did not become actually violent, but required some watching. About twenty months after her operation she committed suicide by hanging.

It is unfortunate that no photographs of this patient were obtained, either before or after operation. The striking thing about this record, of course, is the complete clinical picture of suprarenal hyperfunction, with no pathologic evidence to justify such a diagnosis. However, the fact that the symptoms disappeared entirely after left suprarenalectomy would seem to confirm the clinical diagnosis of cortical hyperfunction and to point out the fact that such functional disturbance may exist in the absence of any morphologic change in tissue of the suprarenal gland.

Several other female patients with marked hirsutism have been seen in the clinic. One of them (Fig. 4) had an exploratory operation after return to her home, and the surgeon reported that abnormalities could not be demonstrated in the suprarenal glands or other organs in the abdomen. Carcinoma of the breast appeared later.

Another patient with marked hirsutism had a carcinoma of the pituitary gland, but hyperplasia of the suprarenal glands was also demonstrated at necropsy. Other patients with hirsutism have not had sufficient evidence of suprarenal dysfunction to justify surgical exploration.

Figure 4. Marked hirsutism of a woman. Surgical exploration at the patient's home did not disclose abnormality of the suprarenal glands or abdominal organ.

A number of years ago, at the University of Minnesota, there was a patient whose clinical course was almost identical with that of Feinblatt's patient. Dr. Bell has kindly furnished the records of the case.

The patient, aged forty-two years, was the mother of two children. She had complained of abdominal distress for about two years, and one year before her examination had noticed increased growth of hair which finally had necessitated her shaving. Ascites and edema and amenorrhea had been present for seven months. There was marked atrophy of the breasts. She was extremely emaciated, asthenia increased gradually, and mental confusion developed before her death. Necropsy revealed a malignant hypernephroma of the left suprarenal gland, with metastasis to the liver, lungs, right suprarenal gland and regional lymph nodes.

During the current year Dr. Berglund has had under his care a young woman, nineteen years of age, who has the typical syndrome of cortical tumor. This patient was seen with Dr. Berglund by one of us. He has been kind enough to send a photograph (Fig. 5), together with a brief record of the case.

Six years ago the patient had the left foot amputated for a reddish black tumor. After this operation, menstruation ceased, and there was rapid gain in weight of about 20 pounds. At the time Dr. Berglund first saw her this year, her weight was 222 pounds. The breasts had not increased in size in proportion to the rest of the body. One year after amputation of her foot, her voice became coarser, there was increased growth of hair on the face, and in the last two

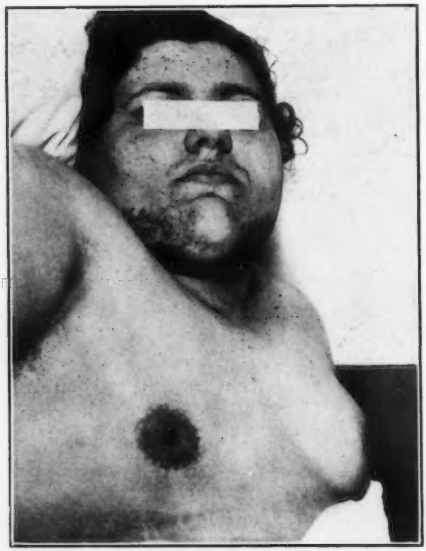


Figure 5. Obesity, hypertrichosis, small breasts, and brownish pigmentation around nipples and in axillae, of a woman aged nineteen years. Typical syndrome of cortical tumor. Roentgenologic examination gave evidence of multiple metastatic tumors of the skull, vertebrae and lungs.

years the hypertrichosis had become more extreme, so that shaving had been necessary. Clinical examination revealed evidence of multiple metastic tumors in the skull, vertebrae, and lungs. The blood pressure was normal. There was also brownish pigmentation of the type seen in acanthosis nigricans around the nipples and in the axillae. Deep roentgenologic treatment was followed by some general improvement, and by reduction of the size of the tumors in the lungs. The patient lost about 20 pounds in weight during the treatment. At necropsy a hypernephroma was found.

In our classification of syndromes resulting from changes in the suprarenal glands, the pathologic basis for cortical hyperfunction has included hyperplasia, and carcinoma or hypernephroma. All grades are found, from small, benign adenomatous growths often discovered accidentally at necropsy to large necrotic, infiltrating and metastasizing neoplasms. In considering the cases of cortical tumor reported in the literature, in some the growths have been highly malignant, with early metastasis, but in other instances no extension of the growth has occurred. Metastasis, if present, is most common in the lungs, bones and liver. The presence of metastatic growths in the lungs or bones can readily be detected by careful roentgenographic studies. In the liver, metastatic neoplasms result in retention of the bromsulphthalein out of all proportion to the extent or number of the growths. However, most of the patients who have died after surgical removal of cortical tumors have done so soon after operation and without evidence of metastasis (31, 66). It has been pointed out that in the majority of cases of suprarenal neoplasm involving the cortex of one gland, the gland of the opposite side is poorly developed, atrophied, or

absent.* The presence of such pathologic change is in accord with the mode of death described following removal of tumors. The patients appear to be in good condition for several hours after operation, but begin to fail rapidly. The pulse becomes rapid and very weak, the blood pressure drops, drowsiness ensues (it is the picture of suprarenal insufficiency), and death follows.

In such cases the shock probably results from suprarenal insufficiency. It is possible that with an adequate supply of the cortical hormone, such operation may be undertaken in the future with far less risk than has been possible heretofore.

Medullary hyperfunction. The immediate anlage of the suprarenal medulla lies in the sympathetic ganglions, which in turn are derived from the cells of the neural crest. Tumors of the medulla are of three varieties, depending on the type of cell from which they arise. Thus we have the (1) nuroblastoma or sympathoblastoma, (2) the ganglioneuroma, and (3) the paraganglioma or pleochromecytoma. A classification of such tumors is presented:

Neuroblastoma; clinical types characterized by:

1. Metastasis to liver and lungs or abdominal lymph nodes; Pepper type.
2. Metastatic involvement of orbit, skull, and long bones; Hutchinson type.
3. Severe anemia suggesting the pernicious type (Goldzieher).

Ganglioneuroma:

Rare; usually found incidentally at necropsy.
Metastasis rare.

Paraganglioma may cause:

Intermittent hypertension.
Continuous hypertension, sometimes with diabetes.

In The Mayo Clinic seven children have been observed whose symptoms and physical condition indicated the presence of the Hutchison type of tumor. In six cases only a clinical diagnosis was made, but in one of them, which is typical clinically for the group as a whole, confirmation was found at necropsy. The report of this case follows:

A boy, aged thirteen years, apparently had been well until about six months before his examinations at the clinic, when it had been noticed that small lumps were appearing on his scalp, and he had begun to lose strength and had become increasingly pale. He had been taken to a physician, who had examined his eyes and had said that he had choked disks. Since that time he had grown gradually weaker. His vision had become progressively poorer, and the lumps on his head had continued to increase in size. For about a month before his admission he had been complaining of attacks of pain in his knees and hips. He had not complained of headaches or vomiting.

*Hypertrophy of the suprarenal gland has been observed both experimentally and clinically in cases in which one suprarenal gland has been removed or is absent congenitally. Conversely, with cortical tumors, there is often contralateral faulty development (van den Bergh) or complete absence (Feinblatt) of the gland on the opposite side.

When the patient was examined at the clinic pallor was striking and his skin had a slightly greenish tint. The entire forehead and vertex were covered with nodules, varying in diameter from 2 or 3 to 6 or 7 cm. Some of these nodules were rather soft and others were very hard (Fig. 6). The veins of the

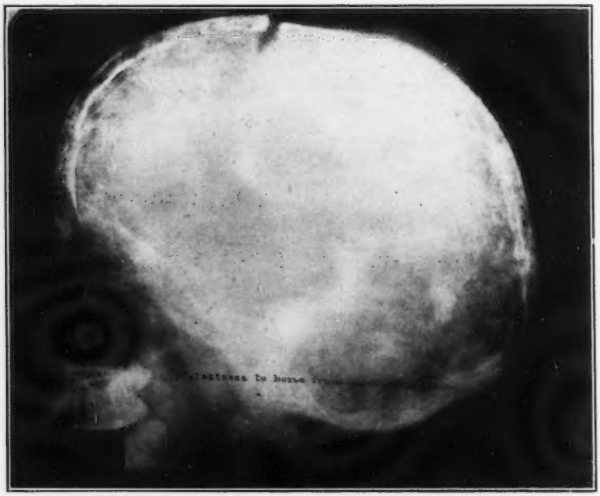


Figure 6. Roentgenologic appearance of skull in case of metastasis from neuroblastoma of left suprarenal gland. The patient was a boy aged thirteen years.

scalp were greatly dilated, and there was moderate exophthalmos. He was extremely emaciated, and his skin was hot and dry. There were hard, rapidly throbbing vessels in his neck. The liver and spleen were palpable and there was marked tenderness over the sternum. Ocular examination revealed choked disks.

The patient was hospitalized and grew gradually worse during the month he was under observation. He then contracted influenza and died. Necropsy disclosed malignant neuroblastoma of the left suprarenal gland, with multiple extensive metastasis to the bones of the skull, vertebrae, sternum, and regional lymphatic structures; bilateral hypostatic disseminated broncho-pneumonia, also, was present.

The other patients of this type all died at home within a few months after they had been examined at the clinic.

In a third and very rare clinical type of neuroblastoma, the symptoms of severe secondary anemia develop and the case may be mistaken for one of pernicious anemia (22).

Ganglioneuromas of the suprarenal medulla are rare, and usually are small, benign tumors which are found at necropsy, having presented no significant clinical picture in life. Occasionally, however, the tumors attain considerable size, and are seen generally before the twentieth year. Gallerstedt and Hjelm, in 1928, reported the case of a boy aged six years, in whose suprarenal region fine, coral-like calcification was seen in the roentgenogram. At necropsy this proved to be calcification of a ganglioneuroma of the suprarenal medulla.

The paragangliomas, or chromaffin cell tumors are the most significant of the medullary group from a clinical standpoint. Berdez, in 1892, was

the first to describe a tumor of this group. Rabin, in 1929, reviewed the entire literature relating to these tumors and found thirty authentic cases. The growths occur not only in the medulla, but also wherever chromaffin cells are found. The tumors are usually benign, and do not produce a cachectic state.

The clinical syndrome which results from the presence of paragangliomas is due, in all probability, directly or indirectly to excessive secretion of epinephrine or of some allied compound. The epinephrine content of the tumors, as shown by chemical and biologic tests, is far greater than that of normal suprarenal glands.

Neusser and Wiesel called attention to the changes of sclerosis due to epinephrine in a child aged two years, with this type of tumor. Vasomotor instability was apparent in Kolisko's case: a man who was apparently healthy and vigorous had a tooth extracted under local anesthesia with cocaine; two hours later he was dead, and necropsy revealed a bilateral suprarenal tumor which contained a great deal of epinephrine. Microscopic examination disclosed that the tumor consisted entirely of pleochrome cells. Labbé, Tinel and Doumer first observed the phenomenon of intermittent paroxysmal hypertension in 1922, and in 1927 a similar case was reported by Oberling and Jung.

Our interest in this type of case was aroused, particularly when we had under our care a patient who was suffering from paroxysmal attacks of hypertension of unknown origin. The presence of intermittent hypertension was detected, and in searching the literature the cases reported by French clinicians were found, suggesting vagal stimulation as the cause. We, on the other hand, felt that the stimulation was of the sympathetic system. C. H. Mayo was called in consultation. Exploration of the left side of the abdomen was carried out, because of the excess of distress on that side, and because of the patient's complaint of persistent discomfort there. The operation was performed by C. H. Mayo, who later reported the case. The history is of unusual interest, and it is now five years since the operation. Therefore it is in part repeated here. There were many difficulties attending diagnosis. In referring the patient to the clinic her family physician wrote: "I feel much as Festus felt in sending Paul to Rome, not having any definite accusation against him."

A woman, a music teacher, aged thirty years, came to the clinic June 2, 1926, complaining of attacks of dyspnea, occipital headache, tachycardia, and vomiting. For eight or ten years previously she had felt "run down," but had carried on her occupation. She had suffered from moderate constipation for six years, and the appendix had been removed three years previously. The paroxysmal attacks had commenced one and a half years previously, and had been increasing in frequency and severity; they had occurred every day or two for periods of from six to eight weeks, each one lasting from a half hour to three or four hours, and being followed by severe prostration. Some blood had been brought up into the mouth, but the patient was not certain whether it was vomited or expectorated. Several infected teeth had been removed, and a rest cure had been followed for eight weeks with doubtful results. The patient was of the asthenic type, undernourished, and somewhat pale.

Because of the uncertainty as to diagnosis in the clinic the patient was placed in hospital for observation. The attacks resembled somewhat those of paroxysmal tachycardia, but study of the blood pressure during attacks demonstrated that within three or four minutes from the onset of the discomfort the systolic blood pressure increased from 80 or 90 to 160 or 180 mm. The heart became enlarged moderately during attacks. It was soon learned that, although the pulse rate was increased in the attacks, the tachycardia was secondary to the increase in blood pressure. The attacks varied in frequency and severity. Consequently, the case was regarded as one of paroxysmal hypertension, a condition not heretofore seen in the clinic.

Operation was performed October 9, 1926, through an upper median line incision. The left suprarenal body was twice normal size, and the right apparently slightly enlarged. There was an oval mass, about 6 by 4 cm. in various diameters, situated retroperitoneally, behind the tail of the pancreas, on the mesial side of the left kidney, and impinging against its upper pole. The capsule of the tumor was opened retroperitoneally and the tumor enucleated intact.

Postoperative convalescence was uneventful for two weeks; then pulmonary infraction developed, the signs of which lasted about ten days. The paroxysms of hypertension did not recur, and after operation the patient was entirely free from the accompanying symptoms; headache, tachycardia, dyspnea, and vomiting. The patient's systolic blood pressure remained about 120, and the general health improved tremendously, so that within six months after the operation her weight had increased about 30 pounds. Within a year after removal of the tumor she had resumed her work teaching music. Recent reports have been received, both from the patient and her physician. In the patient's letter, written May 6, 1931, the following is stated:

"I have been enjoying fairly good health and am able to teach every day. Just before Easter I had a mild attack of the 'flu,' with a heavy chest cold. Since that time I notice the weakness in my right lung more than formerly and have experienced a dull pain in it occasionally. Except for fatigue, I feel very well at the time of writing."

Her physician made a thorough examination. She had no complaints, and all physical findings were essentially normal. There was no evidence of any tumor or of tenderness when the abdomen was palpated. He commented that she had been feeling well for the preceding year and working every day. Her only illness was an attack of influenza which kept her in bed for four days.

Since this first case was reported, two additional cases have been reported in the literature; the first by Shipley and Pincoffs, and the second by Porter and Porter. In each of these cases, a diagnosis of suprarenal tumor was made clinically, and in both instances paragangliomas were discovered at operation, following which the patients were relieved of attacks of paroxysmal hypertension. In the case reported by Shipley and Pincoffs, the patient was a woman, aged twenty-six years. She had complained of attacks consisting of a hot, flushed feeling in both arms, followed by a sensation of tightness about the heart, with palpitation. There was a feeling of difficulty in breathing and of swelling in the neck. Nausea would appear and forced vomiting gave some relief. During the attacks there was some apprehension associated with the marked palpitation, and a general, shaky, nervous feeling. Examination during attacks disclosed a systolic blood pressure ranging from 176 to 260. The situation was complicated somewhat by the fact that a tumor could not be palpated in the abdomen, and so, since in the previously reported cases the tumors had been situated on the left side, the incision was made on the left, but the tumor was found to be on the right side. Since it could not be reached from the incision on the left side, this was closed, and the patient was operated on again, thirteen days later, when the tumor was removed. The patient had

almost daily attacks of paroxysmal hypertension during the interval between the two operations, but these disappeared completely after the second operation. The presence of epinephrine in the tumor was demonstrated by Dr. Schultz.

The patient of Porter and Porter was a man, aged thirty-nine years, who complained of peculiar attacks accompanied by an unpleasant sensation in the epigastrium, "similar to, but not exactly, nausea." Most of these attacks occurred while he was in bed and lasted thirty to forty seconds. His color at this time was ashen. He gradually learned that by inclining forward and to the left he could produce an attack at will. The systolic blood pressure was then observed to rise from 110 to 200 or more within ninety seconds. The cardiac rate slowed to about 55 for each minute, with a very forcible pulsation. The condition lasted three to four minutes, when the pressure dropped as rapidly as it had risen. The diagnosis of probable chromaffin cell tumor was made, and exploratory laparatomy was performed. In this case, the tumor was found on the right side also.

Both Dr. Shipley and Dr. Porter have been kind enough to forward pathologic sections from the tumors in these cases for comparison with the tissue removed from our patient. After examining, and comparing the three sections, Dr. McCarty is of the opinion that all these tumors have arisen from the same embryonic tissue that forms the suprarenal gland. He stated: "Neoplasia is followed frequently by tissue atavism. Therefore any neoplasm having its origin in the primitive cells from which the suprarenal gland is formed normally, might be expected to resemble both glandular and neurocytic tissues."

On microscopic examination, Dr. MacCarty found the whole tumor from our patient to be composed of large, granular, spheroidal cells, frequently distorted, apparently from pressure.

"The bodies of these cells," he wrote, "are about three times the size of the nuclei, which are spheroidal and contain nucleoli, many of which have a diameter one-fourth to one-fifth that of the nuclei. Diffusely interspersed between the spheroidal cells there are numerous fibroblasts and fibrocytes. The fibroblasts also contain very large nucleoli. The pathologic diagnosis is adenoma apparently related to suprarenal tissue. The cytology suggests a neoplasm of low degree of malignancy. The slide of the tumor removed by Dr. Porter resembles almost exactly that of our case just described. The section from the tumor which Dr. Shipley removed appears quite vascular, and glandular elements constitute practically all of the tumor. These cells are grouped, hyperplastic, and very irregular in shape and size. Many contain large nucleoli. The cells of the parenchyma do not look as much like suprarenal cells as those in the other two specimens. In some portions they appear to be fibrocytic in type. The bundles suggest that they may be neurogenic."

In another case, reported by Vaquez, Donzelot and Géraudel, the patient, who was suffering from paroxysmal attacks of hypertension, refused operation, but a paraganglioma of the suprarenal gland was revealed at necropsy. Intermittent paroxysmal hypertension or vascular crises are not always indications of suprarenal tumors. They have been reported as

occurring with mediastinal tumors and pneumonia, and have been ascribed to vagal irritation.

In contrast to the three reports of cases in which removal of suprarenal paragangliomas resulted in relief from the distressing symptoms of paroxysmal attacks of hypertension, we are presenting an additional report. In this instance, the diagnosis of tumor of this type was made clinically, and the patient was subjected to operation, but a tumor could not be found.

A railway brakeman, aged forty years, came to the clinic in January, 1930, complaining of high blood pressure. At the age of thirteen years he had had chorea, and at twenty years, a lesion on his lip, which had been treated by intravenous injections of "yellow medicine." His general health until the onset of the hypertension had been good, however.

Nine months prior to his admission at the clinic, the patient had been told, in the course of an examination, that he had high blood pressure. Since that time he had undergone repeated examinations, and marked fluctuation in blood pressure had been observed. The systolic pressure had ranged from 120 to 210 mm. of mercury. The patient stated that he had been unable to work for nine months, because of attacks of nervousness, tachycardia, palpitation, flushing of the face, and a choking sensation in the throat. The attacks were usually initiated by excitement or exertion and lasted from two to three hours. It had been observed that the systolic blood pressure rose to the neighborhood of 200, while the symptoms were present and frequently subsided to 120, with relief, in two and a half to three hours. For the last two years he had suffered with intermittent attacks of "neuritis" which were characterized by "spot pains," striking and disappearing rapidly in the extremities, involving principally the calves. Definite hyperesthesia persisted over the spots for some time after the pain (Fig. 7).

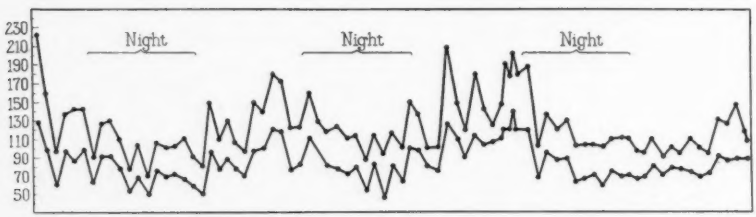


Figure 7. Hourly readings of blood pressure of a man aged forty years.

The man was thin and well-developed, with Argyll-Robertson pupils and diminished knee reflexes. The right kidney was easily palpable, and the smooth edge of the liver was felt just beneath the costal margin. The systolic blood pressure varied from 90 to 235 and the diastolic range was 50 to 125. The laboratory findings were essentially normal. The Wassermann tests of both blood and cerebrospinal fluid gave negative findings. The basal metabolic rate, twice was +21 and +10 per cent; determinations of blood sugar, taken before, during, and after dizzy spells were within normal range; the urine, the blood, and roentgenograms of the thorax and head were normal.

The patient was removed to the hospital for observation, and exploratory operation was decided on, in the hope of finding that the cause of the paroxysmal hypertension was a tumor in the suprarenal region, as had been found in the case which has just been described, and in which the results were so beneficial. Exploration of both renal regions and pancreas by Dr. Judd revealed no recognizable changes anywhere. Both kidneys were movable and free; no lump or tumor was found about them. Shortly after operation the respiratory system began to fail, edema of the lungs occurred, and the patient gradually failed. He died three days after the operation.

After necropsy, the following reports were submitted by Dr. Robertson: "Hypertrophy of the heart (415 gm); multiple petechiae of the brain and cord; bronchopneumonia, and exploration for possible suprarenal tumor was negative." Microscopic sections of the suprarenal gland gave evidence of hyperplasia, but the evidence was not sufficient to account for the symptoms.

This case emphasizes the fact that diagnosis in this type of case may be extremely difficult and fraught with uncertainty. Of course, we cannot say, concerning this case, that even in the absence of evident disease there might not have been some dysfunction of the suprarenal medulla, but the clinical history and other data would suggest such a possibility.

Hypertension and tumors. A cursory review of the literature disclosed reports of twenty-nine cases in which hypertension associated with suprarenal tumor was present. Tumors of the medulla in which this association was noted have been reported by Orth, Wiesel, Bergstrand, Kerppola, Oberling and Jung, Langeron and Delcour, Barker (5), Labbé, Tinel and Doumer, Vaquez, Wichels and Biebl, and Schroeder. Tumors of the medulla which have been successfully removed have been those of C. H. Mayo, Shipley and Pincoffs, and Porter and Porter. Tumors of the cortex associated with hypertension have been reported by Neusser, Bland-Sutton, Bullock and Sequiera, Volhard, Mackintosh, Hoag, Mathias, Oppenheimer and Fishberg, Walters and Keyser, and Murray and Simpson.

Neusser was the first to describe the association of suprarenal tumor with hypertension. Volhard's cases are interesting in that following removal of the tumors the blood pressure returned to normal. A crucial case is the one reported by Vaquez, in which there was no surgical intervention, and the intermittent hypertension observed early in the course of the disease gave way eventually to continuous and permanent hypertension. The three patients with medullary tumor, who were subjected to operation, all have had immediate, complete, and permanent relief. This raises the important question as to the possible relationship of the suprarenal gland to hypertension.

In view of the rapidly increasing number of cases with this association, the whole subject of hypertension in relation to the suprarenal glands should be reconsidered. The cases may be grouped somewhat as follows: (1) those in which paroxysmal intermittent hypertension dominates the picture (usually due to paraganglioma); (2) those in which bodily configuration and changes in the sexual characteristics indicate hyperactivity of the cortex as well, and (3) a group in which glycosuria and hyperglycemia have constituted prominent clinical findings.

Several features of suprarenal disease bear definitely on the subject of blood pressure. Destruction of the gland, as in Addison's disease, leads to hypotension. A potent principle which raises blood pressure has been isolated from the suprarenal glands. Tumors of these glands lead frequently to intermittent or to continuous hypertension, and removal of the tumors results in restoration of normal blood pressure. These are facts and cannot be disposed of readily. It may recalled also that absence of

pathologic evidence for the participation of the suprarenal glands in the pathogenesis of hypertension is no more striking than the absence of pathologic evidence of participation of the islets of Langerhans in diabetes mellitus. We are forced then, we believe, to accept either the view that there is a small and special group of cases of hypertension of which the cause is in the suprarenal glands, or that the suprerenal glands participate directly or indirectly in the pathogenesis of hypertension. With the advent of new active principles from these glands, these viewpoints must be kept in mind. Comprehensive histologic studies are desirable in every case of suprarenal tumor in an effort to relate clinical pictures to types of cells involved.

COMMENT CONCERNING TUMORS

In a study of the cases reported in the literature of tumors of the suprarenal gland, the complexity of the whole problem is especially striking. There are many cases in which the clinical and pathologic data seem to indicate involvement of some particular portion, and even some particular type of cell, and the diagnosis, both clinical and pathologic, is definite and clean cut. In other instances, the complexity of the clinical picture would seem to point to involvement of both the medulla and the cortex. In the two cases reported by Oppenheimer and Fishberg, one of a man aged twenty-four years, and the other of a girl aged twelve years, there were severe hypertension and clinical evidence of cortical dysfunction. In the former case the pathologic examination showed that the malignant process involved both the cortex and the medulla. Another case of this type is the one reported by Murray and Simpson, to which we have already referred. This patient had complete relief from symptoms of virilism after removal of a cortical tumor, but her systolic blood pressure, which before the operation had been consistently high (200 to 120) was reduced to 130 after operation; however, it continued to rise to 190 or 200 on slight excitement. This would suggest that in this case of cortical hyperfunction there may have been, also, some derangement of medullary function. In this connection it is interesting to note that we saw, on one occasion, a sharp rise in blood pressure following administration of cortical hormone to a patient with hypertension. In going over the record of the case reported by Walters and Keyser, the question might be raised as to whether there was some element of medullary involvement. The blood pressure, which ranged from 124 to 180 systolic, and the complaint of intermittent attacks of precordial pain and a jerking sensation in the heart, would suggest that these might have been paroxysmal hypertensive attacks. The increased blood pressure and glycosuria, and the hyperglycemia, bring to mind the clinical picture described by Wiehels and Biebl as being due to paraganglioma of the medullary portion of the gland.

There are cases of tumor of the suprarenal gland in which the pathologist finds it extremely difficult to differentiate the various types of cells. In these cases the clinical findings are difficult to evaluate. In some in-

stances in which various pathologists have examined tissue from a certain growth, there has been disagreement as to the type of cells involved. This was true of the case reported by Anderson, in which tumor of the suprarenal gland was accompanied by fatal hypoglycemia. The patient, a man, aged thirty-three years, was found semi-conscious one morning. He recovered in twelve hours and was well for two days, when he again was semiconscious and experienced some dimness of vision. The physical findings were essentially normal, and he was aroused after administration of 300 cc. of 20 per cent solution of glucose. Two days later he became maniacal and cyanotic and his head was retracted. The concentration of blood sugar was 60 mgm. in each 100 cc. Glucose was administered steadily for two months, but the patient eventually died, presenting the typical picture of insulin shock. Several pathologists gave various versions of the pathologic process involved. Two of them considered the tumor to be cortical and one considered it medullary. Thus the clinical data could not be interpreted adequately.

To summarize, we may say that there are various types of tumors of the suprarenal glands, resulting in a large variety of clinical symptoms and syndromes, many of which are difficult to explain adequately in the present state of knowledge. Correlated clinical, pathologic, and chemical studies are urgently needed.

CLINICAL MANIFESTATIONS OF HYPOFUNCTION

Hypo-adrenalism or hypo-adrenia. Whether there is a clinical state other than Addison's disease that properly can be called suprarenal deficiency or hypo-adrenalism or hypo-adrenia remains open to serious question. Many physicians make diagnoses of this kind without adequate basis. There is a group of patients with exhaustion, chronic fatigue, emaciation, low basal metabolic rate, low blood pressure, and loss of libido and potentia, whose troubles are attributed to suprarenal deficiency. But there is little real proof that the suprarenal gland is responsible.

We have recently endeavored to determine whether such patients are benefited by treatment with the cortical hormone. One of the patients was sent to us by a well-known clinician with the diagnosis of hypo-adrenia. The results of our treatment of this group of patients with the cortical hormone suggests that some other cause than cortical insufficiency is responsible for the clinical picture.

One patient was a man, aged thirty-four years, whose illness had been diagnosed previously as tuberculosis, and he had spent two years in a sanatorium. We had complaints of gastric distress, constipation, exhaustion, and some pain in the thorax. Examination did not reveal evidence of tuberculosis. There was atrophy of the left testis. The systolic blood pressure was 112 and the diastolic 68. He was underweight. There was moderate pigmentation of the skin with black freckles. Improvement did not follow administration of 60 cc. of the cortical hormone.

Another patient of this type was aged twenty-four years. He had been disabled for one year following an acute infection. His complaints were constant aching of the legs and extreme exhaustion, especially after standing. He was very tall and weighed only 130 pounds. The systolic blood pressure was 112 and the diastolic 78. The basal metabolic rate was —18 per cent. There was some pigmentation of the hands and face. The patient was not benefited from treatment with the cortical hormone.

Mills, who reported a group of patients studied in China, in which a diagnosis of hypo-adrenia was made, noted some improvement in symptoms following administration of epinephrine. His results would suggest that these patients had been suffering from deficient function of the medullary portion of the suprarenal gland. However, in our hands, neither epinephrine or the cortical hormone has proved of any considerable value in cases of so-called hypo-adrenia.

Addison's disease. The successful isolation of the cortical hormone of the suprarenal gland by Swingle and Pfiffner (58, 59, 60) has stimulated interest in the treatment and further study of Addison's disease. As we all know, this disease is due to decrease, or lack of secretion, of the hormones of the suprarenal glands. Any pathologic lesion which gradually destroys the suprarenal bodies may produce the characteristic syndrome of Addison's disease, at least in part. It may be recalled that the complete clinical syndrome has never been produced experimentally, although recent work indicates that this may possibly be accomplished. Practically the only pathologic lesions of the suprarenal glands which one may expect to encounter are tuberculosis and simple atrophy, the former accounting for about 90 per cent of all cases. However, it has been claimed that authentic examples of the disease have been described as the result of carcinomatous deposits in the suprarenal glands, amyloidosis, gumma, destruction by hemorrhage or infarction, with replacement by scar tissue, chronic inflammation with secondary fibrosis, mycosis fungoides, and lesions of the semilunar ganglions, celiac plexus, and the abdominal sympathetic chain without evident involvement of the suprarenal glands. The latter group of cases, in which the suprarenal glands apparently have been normal, are found reported principally in the older literature. These reports are responsible for the long controversy which arose over the relation of the suprarenal glands to the syndrome of Addison's disease. That irritation or interruption of the sympathetic nervous system is responsible for some of the symptoms of the disease can hardly be questioned. Nevertheless, it is the opinion of modern observers that the essential basis for the syndrome which Addison described lies in loss of function of the suprarenal gland alone. Despite all that has been said and written, the majority of cases of Addison's disease are due to tuberculosis or atrophy.

In a large proportion our cases which came to necropsy, bilateral, caseating tuberculosis of the suprarenal glands was revealed. In a few

there was simple atrophy of the gland. Seventy cases in which other suprarenal lesions were found at necropsy also have been analyzed by Barker (6); these lesions include carcinoma, periganglioneuroma, amyloidosis, and hemorrhage. In none of this group did the clinical syndrome correspond to that described by Addison. Attempts have been made to establish a syndrome definitely related to the type of lesions present in the suprarenal gland. So far as we know, this is not possible; the cases of atrophy and tuberculosis run almost identical courses. It is of interest that pigmentation is more uniformly present in cases of suprarenal atrophy than in those in which the underlying factor is tuberculosis; also, on the average, length of life is apparently somewhat longer in cases of atrophy. Otherwise, the clinical course is practically identical in both groups.

According to Guttman, "Following destruction of the medulla only, the cortex may function and prevent symptoms of the disease. It is also clear that all symptoms of the disease may be clearly manifest in cases in which the cortex is destroyed and the medulla is intact. However, it cannot be denied that, for the normal function of the gland, the two parts are essential and act synergistically. There are several reasons why this may be so. Biedl has stated that the peculiarity of the vascular supply and the ontogenetic and phylogenetic development of the suprarenal glands suggest a functional relationship between the cortex and the medulla. Landau has stated that, in the development of the gland, the infolding of the cortex suggests a functional relationship between the cortex and the medulla, as in this way a larger surface of the cortex is brought into apposition with the medulla. Recently Wayman cited evidence that the cortex is concerned with the steady maintenance of certain bodily functions, whereas the medulla brings about rapid adjustments under certain conditions. Cremar claimed that he was able to trace a functional relationship between the cortex and the medulla by using stains by which he was able to trace the functional activity of the gland. Hartman and Hartman, using the Folin, Cannon, and Denis calorimetric test, the inhibition of intestinal contraction test, and the denervated iris test have found that epinephrine is present in the cortex.

It is probable, therefore, that an anatomically intact medulla may not function normally when the cortex is the seat of marked destruction. It is also likely that the extreme variability of symptoms observed in cases of primarily contracted suprarenal glands may be due to varying degrees of disturbance in the synergism of the cortex and medulla. However, if this relation is shown not to exist, we must fall back on the theory that the destruction of the cortex alone is responsible for all the symptoms of Addison's disease.

Before considering the results of treatment, something should be said concerning the signs and symptoms of Addison's disease. The disease can be considered in three phases: (1) the early phase, or state of development, in which the disease is, as a rule, latent; we have raised the question

elsewhere of whether the infection of the upper part of the respiratory tract, referred to as influenza, and which initiates the disease in so large a proportion of cases, may not be an acute febrile phase of the disease itself, since many of the patients never recover their strength until the onset of pigmentation, weeks, months, or even years later; (2) the phase in which the disease is usually recognized; it consists of the classical picture outlined by Addison and familiar to us all, and (3) the final phase is the stage of collapse, in which, as a rule, nausea and vomiting are extreme, dehydration develops, and there is circulatory failure; this picture is seen not infrequently in the course of crises, and also as the terminal phase of the disease.

The most prominent symptoms and signs of the disease are asthenia, fatigue, pigmentation, anorexia, nausea and vomiting, loss of weight, attacks of dizziness and syncope, arterial hypotension, dehydration, and circulatory failure. Asthenia and fatigue are the most common early manifestations. These progress more or less rapidly in individual cases. Pigmentation may appear early, and may persist for months or even years prior to onset of the other signs and symptoms. Marked and prolonged pigmentation, developing as the sole manifestation of the disease, indicates, as a rule, a favorable prognosis. The combination in the Nordic individual of the quartet, dermal, buccal and labial pigmentation, with the development of black freckles, is almost pathognomonic of the disease. It almost invariably points to the correct diagnosis. Occasionally, anorexia, nausea and vomiting are the initial symptoms. This trio, associated with loss of weight and evidence of circulatory failure and collapse, completes the picture. The development of dehydration and of failing function of various organs is characteristic of the crises and terminal stages.

A new development of diagnostic significance should be mentioned: the roentgenologic evidence of calcification of the suprarenal glands which can be readily elicited in a considerable number of cases of Addison's disease. Although roentgenologic shadows interpreted as calcification were described in 1914 by Rolleston and Boyd, the roentgenogram has not proved of significance in the study of Addison's disease until much more recently. A few desultory reports covering about nine cases in all are to be found in the literature. Recently, Ball, Greene, Camp and Rowntree have presented reports of six cases in which positive roentgenologic shadows of calcification in the suprarenal glands of patients with Addison's disease were obtained. In a series of glands removed at necropsy, it was found that calcification, demonstrable by roentgenogram, was present in 26 per cent of a series of thirty-four cases. Among nineteen clinical cases of Addison's disease, evidence of calcification of the suprarenal glands was found in six, a percentage of 31.5 per cent. In some instances this additional evidence is sufficient to establish the diagnosis definitely.

In one case roentgenoscopic studies were made, and the shadow of calcification was readily seen and definitely located. The movements of the

gland with ordinary respiration, and with forced inspiration and expiration, were noted and charted. The results were subsequently substantiated by roentgenograms. This, so far as we are aware, is the first record of fluoroscopic visualization of the calcified suprarenal gland.

The indications for a grave prognosis might be listed as follows: extreme asthenia, lowered bodily and surface temperature, collapse, protracted vomiting, extreme loss of weight, systolic blood pressure of less than 70 millimeters of mercury, concentration of urea of more than 60 mgm. per 100 cc. of blood, a short rapid course without much pigmentation, poor response to treatment, and active tuberculosis. Rapidly proggressing cases, without much pigmentation, and with a short history, are frequently missed by the clinician and are diagnosed at necropsy. Failure to respond to treatment obviously is significant. The most important single clinical prognostic index is the body weight. Only those who eat and gain in weight, recover.

The chief considerations in treatment are: (1) general care, including physical and mental rest, quiet, a diet with adequate fluids, and symptomatic relief; (2) prevention or treatment of dehydration; (3) substitution treatment with the cortical hormone and the Muirhead regimen, and (4) care of underlying disease and of complications. General care is just as important as formerly. We have learned something in the past few years concerning means of combating dehydration. For substitution treatment, the cortical hormone is the method of choice, but when it is unavailable the Muirhead regimen should be carried out. The care of underlying disease, particularly tuberculosis, still constitutes a tremendous problem. At the present time we are investigating the effects of application of roentgen rays over the suprarenal glands, and administration of calcium and cod liver oil.

We have had twenty-three patients with Addison's disease under treatment with the cortical hormone. Immediate results were excellent in seventeen of these. Three patients died at home, and three while being cared for by the clinic. Of the three who died at home, two responded admirably to treatment while they remained at the clinic, but died weeks or months later, without further treatment. The third patient who died at home was given only a small amount of the cortical hormone when he was under the care of the clinic last summer. He returned home to pursue the Muirhead treatment, and apparently did well for a time. About nine months after his visit to the clinic we were notified by his home physician that he was in crisis, and a supply of the hormone was sent by air mail, but reached him at a time when he was moribund and when, according to his home physician, nothing could have been expected to do any good.

Of the three patients who died while being cared for at the clinic the first arrived at a time when there were three other patients also waiting for treatment, and the total supply of hormone was 40 cc., less than enough for one patient. However, 20 cc. was given to this patient with what appeared to be slight improvement, but death ensued within a few hours. The

second patient was given a course of treatment with satisfactory results, but because of lack of cortical hormone was given treatment with another product which proved ineffective, and while he was receiving it his condition became critical. Treatment with the preparation of Swingle and Pfiffner was again instituted, and he was given 40 cc., but without satisfactory results. We might claim that these deaths were due to inadequate treatment and that with a larger supply of hormone available, these patients might have been saved. This, however, is a precarious position to take, and hence we must list these cases as failures of attempts at treatment.

The case of the third patient who died while under treatment at the clinic is particularly instructive. We were notified of her coming, met her on arrival, and started treatment early, but with results that were disappointing from the start. In fact, following each dose of the cortical hormone, untoward symptoms were observed, in the nature of chilly sensations, tremor, increased nausea, and extreme weakness. It was felt that the source of supply might be important in this reaction, and hence a supply was obtained from Swingle and Pfiffner, with results identical in every respect. This patient had, in our opinion, an adequate amount of the cortical hormone, but continued to fail and died the typical death of Addison's disease in spite of all efforts. This case must be regarded as an instance of failure in treatment with cortical hormone. At necropsy the gland was markedly atrophied, but the histologic changes were different from any previously observed by Robertson. There was also definite hypoplasia of the thyroid gland.

Thus, of the six deaths in our series, four patients received some treatment just prior to death, but only one had what we would consider adequate treatment.

The important clinical changes observed during treatment are the disappearance of anorexia, nausea, vomiting and pain; development of hunger, and a return of normal gastro-intestinal activity; relief from fatigue, and improvement in sleep; increase in strength and endurance; increase in weight; decrease in pigmentation; change in mental attitude, with access of hope and euphoria; increase in blood pressure, although slight and secondary; resumption of normal functions and desire to return to work, and increased resistance to infection, the effects of surgery and drugs.

The disappearance of anorexia, the return of hunger, and the improvement in digestive functions are striking beyond all belief. The results in Addison's disease suggest that the cortical hormone exerts a fundamental influence from the standpoints of hunger, of activity of the digestive tract, and of generation of muscular energy. The psychic effects are very marked and constitute new problems. Before the advent of this treatment our patients had not been eager to return to work, but many of them, under this treatment, have felt a keen desire to return to some occupation.

The significant changes in laboratory and metabolic data resulting from treatment are increase in the basal metabolic rate; gain in weight; improved renal function with disappearance of nitrogen, urea and sulphate retention in the blood; disappearance of creatinuria, and disappearance of achlorhydria.

A brief outline of one of our cases of Addison's disease, which is typical for the group as a whole, is given here:

An aviator, aged twenty-six years, was admitted to the clinic February 16, 1931, with a complaint of weakness and dyspnea on exertion. He dated the onset of these symptoms back ten years, at which time he had been unable to play a complete game of basketball because of exhaustion. Fatigue, dyspnea, increasing pigmentation, and black freckles had been noted, especially in the last year. Seven months before we saw him he had begun to have periodic attacks of nausea, vomiting, and anorexia, and during this period he had lost 25 pounds in weight, and had been fatigued. Physical examination disclosed diffuse olive-tan pigmentation, accentuated over the exposed parts, nipples, axillae, abdominal scar, and genitalia. There were also innumerable, scattered black freckles, but there was no pigmentation of the buccal mucous membrane. The blood pressure ranged from 100 to 120 systolic, and 70 to 80 diastolic. Roentgenograms of the suprarenal region gave evidence of a small calcified lesion on the right.

Under treatment with the cortical hormone, the patient gained strength, became active, his appetite increased, and he gained 17 pounds in weight. He was dismissed and advised to take 5 to 10 cc. of cortical extract twice a week. He followed this regimen for a considerable time, but recently has been able to get along without treatment, and has resumed his occupation of flying. The question naturally arises as to whether he has entered a remission and, if so, whether it is spontaneous or induced.

In considering our results in treatment with the cortical hormone, several factors should be remembered. First, the method of standardization of the preparation has not been perfected and there has been no way to measure the potency of the product in accurate units. Furthermore, as pioneers in this field, we have had to find our way as to dose and the best methods of administration. In all probability we have not yet discovered the optimal treatment. Another fact of paramount importance is that the supply has been entirely inadequate, despite every effort of Swingle and Pfiffner to send us as much as possible. In addition, the shipments have been made at irregular intervals, so that it has been impossible to follow any definite plan of procedure. In the past few months our supply has been augmented by some material from Parke, Davis & Company. The patients have, for the most part, remained at the clinic for only relatively short periods, and have returned home, following a course of treatment, to be cared for by their home physicians. Because of our own meager supply, it has been absolutely impossible to send them amounts sufficient for really adequate treatment.

We must emphasize, again, that the results we have reported are only immediate results, and that observation over years will be necessary to determine the ultimate value of the cortical hormone in the treatment of Addison's disease. Once the hormonal deficiency is adequately covered the problem becomes one of treatment of the tuberculosis.

SUMMARY

The functions of the suprarenal glands are touched upon and the active principles or hormones already isolated, epinephrine from the medulla, hexuronic acid and the cortical hormone from the cortex, discussed. The diseases of the glands may be classified under overactivity and underactivity. Tumors result in pseudo-hermaphroditism, pubertas praecox, virilism and hirsutism, depending on the age at which overactivity develops. Medullary tumors are of three types, neuroblastomas, ganglioneuromas and paragangliomas. The neuroblastomas metastasize freely. The paragangliomas are discussed in some detail. The first case recognized in life and subjected to cure through surgery is discussed. This is a case that was studied by Dr. Rowntree and Dr. Mayo. Certain clinical manifetations received considerable discussion, among others the marked increase in weight often seen in tumors of the cortex, occurring despite many metastases. There is a consideration of the significance of intermittent hypertension with medullary tumors, the appearance of hypertension in certain cases of cortical tumor and the disappearance of this hypertension with removal of the tumor concerned.

In relation to hypofunction two case reports are given of patients diagnosed as having hypoadrenalism or hypoadrenia in which no improvement was noted by administration of adequate amounts of cortical hormone. Addison's disease is presented in some detail from both the clinical and laboratory points of view. In the latter connection the value of x-ray studies in determining calcification of the gland is emphasized. The immediate results of treatment with the cortical hormone of Swingle and Pfiffner, eschatin, are presented. In 23 cases studied all but one responded with immediate results considered satisfactory, provided the patient was in reasonable physical health at the beginning of the treatment and the adequate hormone available. Even when hormone deficiency can be adequately maintained in Addison's disease the physician still faces the problem of the chronicity and of the tuberculosis.

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EFFECTS OF URINARY HEBIN UPON IMMATURE MALE RATS*

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Since the completion of this work a paper by Engle (1) has appeared in which results were obtained that are in practical agreement with our findings. The question of the effect of gonad-stimulating hormones upon spermatogenesis is a fundamental one, since, if it can be demonstrated with certainty that sexual maturity in the male is not hastened as a result of its introduction doubt must exist as to the production of true sexual maturity in the female. Our studies have been made on a larger number of animals and cover a wider interval of time than those of Engle. In view of these facts we believe publication of our results will not be considered superfluous.

The literature on this subject has been fully reviewed by Engle (2) and need not be discussed here.

METHODS

In this study male rats between the ages of twenty and fifty days were killed at the rate of two every three or five days. The testes were weighed and immediately placed in fixing solution. These constitute the controls. Four animals of exactly the same age, some, but not always all, being from the same litter as the corresponding controls, were injected daily with urinary hebin (the name adopted by Van Dyke to designate the gonad-stimulating substance obtained from pregnancy urine), two with 1/5 cc. and two with 1/2 cc. These animals were killed at the same time and treated in the same manner as were the controls. We therefore have three parallel groups running from the twentieth to the fiftieth day of life, a control group, a group having received 1/5 cc. hebin since the twentieth day of life and a group having received 1/2 cc. hebin over the same period. This permits a comparison at three to five-day intervals between normal testes and testes from animals receiving a gonad-stimulating hormone.

Urinary hebin was prepared as follows: Human pregnancy urine was made acid to Congo red with acetic acid; evaporated to 1/5th its original volume; made up to its original volume with alcohol; shaken and allowed to stand; filtered to obtain the precipitate, which was then extracted several times with ether and then dried. It was then redissolved in water, reprecipitated with alcohol, washed with ether, dried and again dissolved in water in such amount that one cc. equalled 20 cc. of the original urine.

*This investigation was aided in part by a grant from the National Research Council, Committee on Research in Problems of Sex.

RESULTS

Our findings are in quite uniform agreement with those reported by Engle. Table I shows the average weight of the testes and it will be noted that those of the injected animals show only a slight increase. The volume of the seminal vesicles of these animals was about five times that of the controls.

The series of histological sections permits a comparative chronological study, at three to five-day intervals of the control group and the groups receiving urinary hebin. The findings were so unequivocal that publication of the entire series seems unnecessary. Figs. 1, 2 show the testis of a

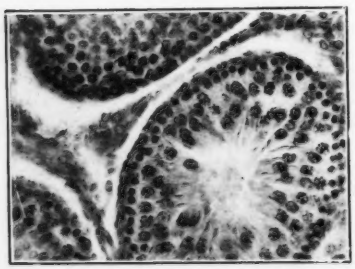

Figure 1. Testis of Injected Rat, 40 days old. Had received ½ cc. Hebin daily for 20 days.

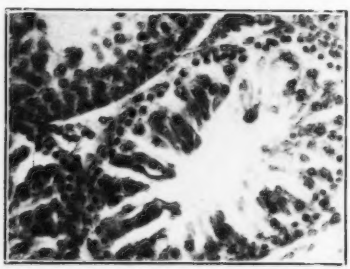

Figure 2. Testis of Control Rat, 40 days old.

normal rat 30 days old as compared with a litter-mate control having received one-half cc. hebin for ten days, and Figs. 3, 4 show a similar comparison of forty-day-old rats, the injected animal having been treated for twenty days. It will be noted that the state of spermatogenesis is the same in comparative animals; the same statement holds for the entire series. Young sperm make their first appearance at about the fortieth day and are mature by the fiftieth day in all groups.

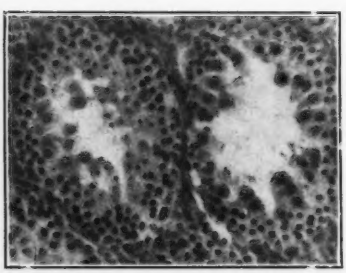

Figure 3. Testis of Control Rat, 30 days old.

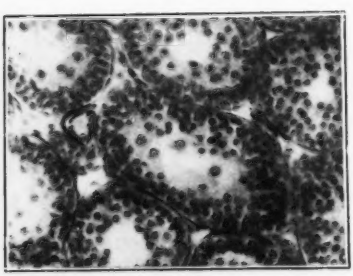

Figure 4. Testis of Injected Rat, 30 days old. Had received ½ cc. Hebin daily for 10 days.

TABLE I

Ages	Control Average	1/5 cc. Average	1/2 cc. Average
20 days	.083 Gm.	.....	.....
25 days	.321 Gm.	.380 Gm.	.422 Gm.
30 days	.363 Gm.	.388 Gm.	.480 Gm.
35 days	.561 Gm.	.509 Gm.	.526 Gm.
40 days	.820 Gm.	.912 Gm.	.944 Gm.
45 days	1.421 Gms.	1.400 Gms.	1.468 Gms.
50 days	1.530 Gms.	1.621 Gms.	1.542 Gms.

DISCUSSION

The most outstanding effect of the administration of gonad-stimulating hormone in the male is the enormous increase in size of the seminal vesicles and the prostate gland. It is well known that the development of these structures is dependent upon the male sex hormone and it would therefore appear that the function of the gonad-stimulating hormone, since spermatogenesis is not hastened, is to increase the output of the sex hormone. The increased amount of interstitial tissue produced supports this view.

Engle (3) has expressed the belief that the effects in the female are essentially the same as in the male, that is, to bring about an increased production of the gonadal hormone. We believe this to be the case. The normality of the so-called precocious maturation of the ovary may well be questioned. If we assume that the function of the anterior lobe hormone is to bring about an increased output of the gonadal hormone then its action upon the ovary should be to cause follicular development, this resulting in an increased estrin production. Some of the follicles so produced might reach maturity and rupture, being followed by the formation of corpora lutea. Others might never reach the stage of rupture and atretic corpora would result. But in no case has ovulation, as such, been the object of the follicular development and in no case of which we are aware have animals brought to maturity in this way become pregnant. Our own experience has been entirely negative. Such animals would breed but apparently did not conceive. It is possible that a certain amount of somatic growth may be necessary before an animal can become pregnant. On the other hand, it may indicate immaturity of the ovum. We are inclined to the latter view and believe that ovulation is merely incidental to the follicle growth, which, as indicated, is solely for the purpose of producing larger amounts of estrin.

SUMMARY

Beginning on the twentieth day of life a series of male rats was injected daily with one-half cc. of urinary hebin (the equivalent of 10 cc. of pregnancy urine). Another group was injected with one-fifth cc. (equivalent to 4 cc.), and a third uninjected group used as controls. The period of injection was thirty days. At intervals of three to five days

during this period two representatives of each group were sacrificed. The testes were weighed and seminal vesicles measured. This permits a comparison at frequent intervals of normal testes with testes from animals injected over varying periods of time with urinary hebin. The following results were obtained:

1. There was no detectable hastening of spermatogenesis.

2. The testes of the injected animals disclosed a larger amount of interstitial tissue than did the controls.

3. The average weight of the injected testes was somewhat greater than that of the controls.

4. The seminal vesicles of the injected animals were greately enlarged.

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THE POLARIZATION CAPACITY OF THE SKIN AS AN INDEX OF THYROID FUNCTION

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The electrical properties of the body (skin, muscles and nerves) have been the subject of investigation of many physiologists. duBois-Reymond (1) some 80 years ago dealt extensively with electrophysiology in man and in the experimental animal. It was Féré (2) who pointed out that the emotions will cause a variation in the electrical state of the skin. This he determined by noting galvanometric deflections when a weak electric current was passing through the body while psychic stimuli were applied. Tarchanoff (3) used no external current but attached two non-polarizable electrodes to different parts of the body. The person was subjected to psychic stimuli; by means of a galvanometer connected with the electrodes he showed deflections, especially when one electrode was placed on the palm of the hand, sole of the foot or axilla. Tarchanoff concluded that "galvanic phenomena observed in the skin, which are concomitant with different kinds of activity, should be considered as due to an active state of sweat glands which at this time produced a secretory current"(4).

The phenomena of Féré and Tarchanoff were reinvestigated in 1906 by Müller (5) and Veraguth (6). The latter designated it as the psychogalvanic reflex.

The psychogalvanic reflex has been extensively studied by numerous investigators in both normal and abnormal states, such as, in hypnosis and psychoses [Moravcsik (7), Georgi (8), Peterson and Yung (9), Richter (10), Syz (11) and others].

Gildemeister (12) demonstrated that the impedance of the skin of animals as well as that of man is not a pure resistance but possesses in addition a capacity component which he defined as electrochemical or polarization capacity. According to him the body simulates a polarized electrolytic cell. In a polarized electrolytic cell the electrical impedance comprises a resistance component due to the resistance of the electrolyte and a capacity component including the ordinary electrostatic capacity due to the specific inductive capacity of the electrolyte and a polarization capacity which is due to separation of the electrolyte and the electrodes by a film of microscopic particles. Gildemeister has called the capacity component of the body impedance its "polarization capacity." The seat of the polarization phenomenon lies in the cell surface, particularly the surface of the

skin cells. The chemistry of the skin polarization process is not well known. The physics of it, however, has been worked out (13). Under certain conditions the concentration of ions on the surface of the cells is altered. Because of these alterations there is a variation in the magnitude of the polarization capacity and the resistance. If one measures the resistance of the skin to alternating current by the usual Kohlrausch method (employing a Wheatstone bridge and telephone receiver), it is not possible to obtain a sharp balance point. Gildemeister (14) has shown that this is due to the polarization phenomena of the skin. It is possible to get a sharp minimum tone in the telephone receiver by inserting at the proper point in the circuit a variable self inductance or a condenser. Thus a modified Wheatstone bridge adapted to a simultaneous measurement of capacity and resistance may be used for measuring the skin impedance. Results may be expressed in the standard electrical units—microfarads of capacity and ohms of resistance.

The electrical capacity of animal organs has been discussed in a preliminary report by Crile, Rowland and Crile (15). They have concluded that capacity of certain organs and tissues of rabbits is constant and is susceptible to change under varying conditions.

Gildemeister (16) has estimated the capacity of the human body, especially of the skin. He found that the capacity in most parts of the skin is relatively constant. For each square centimeter of electrode area the capacity measures 0.01-0.03 microfarads. In a group of 16 healthy adults we found an average capacity of 0.36 microfarads using silver electrodes 12 sq. cm. in size on the forehead and 1000 cycle alternating current.
rent.

The conditions under which measurements are made must be constant. The size and character of the electrodes; the frequency of the current; and the temperature of the skin will influence the readings. Besides these physical factors it was also shown that the application of chemicals, such as tincture of iodin, and alkalis tends to increase the skin capacity (17).

An interesting observation has been made by Lueg (18) that the skin capacity of patients with exophthalmic goiter is increased, while in myxedema the capacity is diminished. This is in accordance with the views of Crile that iodin affects the electric conductivity and capacity of various animals and plants. In clinical terms of Crile: "If too much iodine is present in the organism, the conductivity, capacity, potential and chemical activity of the various organs and tissues of the body are abnormally increased" (19).

The observation of Zondek (20) and Burlage (21) that the electrocardiographic tracings of patients with myxedema show a flattening of the P and T waves is of significance in this connection.

Lueg (22) pointed out that the flattening of the waves is due to changes in the skin capacity in patients with myxedema rather than to electrical changes of the heart.

It is the object of the present communication to report a comparative study of the skin capacity and the basal metabolic rate in a group of 36 patients in whom a thyroid gland disorder was clinically suspected as the cause of the underlying symptoms. This group of cases is selected from a total of 67 patients upon whom the comparative study was made. The remaining patients comprised persons with asthma, cholecystitis, cardio-renal disease and diabetes mellitus. The basal rate and the polarization capacity of the skin in this latter group yielded figures which varied slightly from the normal.

The patients were from the Temple University Hospital and Medical Service No. 1 of the Mount Sinai Hospital of Philadelphia.

Method: The patients were examined in a fasting state, abstaining from food or liquids for twelve hours. A large number of these patients were in the hospital over night or when ambulatory, rested in bed for one and a half hours before the test. For the basal determination a Sanborn-Benedict portable apparatus was used. In nervous and apprehensive patients the test was rechecked the following morning. A twenty-minute rest period was given after the basal rate determination before measurements of the skin capacity were made. For the latter a Farad bridge was used, supplied by Leeds & Northrup Co., of Philadelphia.

See Diagram 1, Page 302.

The Farad bridge comprises a standard capacitance, a standard series resistance, and a continuously variable slide wire used for the ratio arms. The slide wire is used to find the ratio existing between a standard impedance and an unknown impedance. In the measurements the unknown impedance is the human body. Since the human body is not a pure capacitance, it is necessary to place a resistance in series with the standard capacitance in order to obtain an impedance having a resistance component simulating the apparent resistance component of the body impedance. For each measurement three observed values were kept:

I. The bridge ratio;
II. The value of the standard capacitance in microfarads;
III. The value of the series resistance in the standard arm in ohms.

The product of I and II is the apparent capacitance of the human body, and the product of I and III is the apparent resistance when the body is considered equivalent electrically to a resistance and a capacitance in series.

Source of Current: A microphone hummer delivering 6 volts at 1000 c.p.s. was used as the source of current. Telephone receivers were used as detectors.

We are indebted to Leeds & Northrup Co. for many valuable suggestions regarding the electric measurements made during the study.

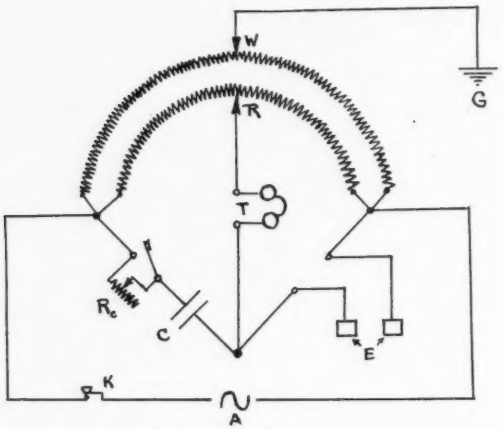

DIAGRAM 1

G—Ground.
W—Wagner Earth.
R—Ratio Slide Wire.
Rc—Resistance in Series with Capacitance.
T—Telephones.
C—Standard Capacitance.
E—Electrodes.
K—Key for Current Control.
A—Source of High Frequency Current.

It is known from the theory of the capacitance bridge (Laws, 23) that when measuring an impedance consisting of a capacitance and resistance connected in series a balance is obtained if the capacity component of the unknown impedance is equal to the product obtained by multiplying the capacitance standard by the bridge ratio and the resistance component of the unknown is the product of the series resistance in the standard side of the bridge multiplied by the bridge ratio. It may, therefore, be stated that the human body behaves electrically as though it were composed of a resistance and a capacitance connected in series, and it is this impedance that was measured with the apparatus.

The impedance calculated from the bridge reading is definitely the value of pure capacitance and pure resistance, which, when connected across the X terminals, would balance the bridge at the same point as did the human body with the electrodes connected at particular points.

Two silver electrodes, each 12 sq. cm. in size, were used. One electrode was applied to various parts of the body to be measured. To obtain better contact a piece of filter paper the size of the electrode wetted in 1 per cent NaCl was placed between the electrode and the skin. Equal pressure was applied to the electrode by means of a leather belt. The other electrode attached to the right hand was placed in a 2000 cc. glass jar containing tap water at 98° F., as recommended by Lueg (24). The following parts of the body were measured: The forehead, left chest anteriorly, inner aspect of the left forearm, the left thigh and the inner aspect of the left lower leg. The summation of the readings of the first three areas is designated as the upper measurement, the summation of the readings of the last two is designated as the lower measurement.

In making skin capacity readings erroneous results may be obtained when the electrode is not properly applied or when the part of the body is hairy or the skin cracked or inflamed. The right hand must be immersed deeply in the water. More recent experiments indicate that a bridge containing fixed ratio arms and variable resistances and capacitances in parallel gives comparable results and facilitates operation.

Throughout this study the upper measurement was taken as an index of comparison with the basal rate; in the table the summation of the lower measurement is indicated in column ten. The following example illustrates the method of recording the readings:

Mr. H. H. Age, 44 years. Diagnosis: Masked thyrotoxicosis.

Results: Upper measurement, 1.25 microfarads; lower measurement, 0.57 microfarads.

The resistance was found to be too variable a factor to be of any clinical value; it was therefore omitted in the final calculation.

In a group of sixteen healthy young adults the upper measurement varied between 0.75 and 0.8 microfarads, and the lower measurement (average of readings of forehead, chest, forearm) from 0.35 to 0.45 microfarads. These average figures were taken as a normal standard and the deviation from these as determined on the patients was expressed in percentage in Table I, column nine.

The essential points of the cases studied are given in Table I.

COMMENTS AND CONCLUSIONS

The group is too small to permit definite conclusions. However, it would appear from this study that in a large majority of this series of patients with thyroid disturbance the elevation of the basal metabolic rate was accompanied by a high polarization capacity of the skin and vice versa. Patients showing a low basal rate yielded a low polarization capacity of the skin. It is noteworthy that in some instances the basal metabolic readings markedly differed from the polarization capacity. When the tests were rechecked the error proved on the side of the basal rate rather than with the polarization capacity. In the table only the figures obtained after the rechecking of the readings are indicated. The level of deviation from the normal as expressed in percentages were not always parallel. It must be borne in mind that neither method is devoid of error. It is a well-known fact that nervousness and apprehension, or at times a desire to urinate during the test may yield an elevated basal rate. This might explain the 95 per cent increase in the basal rate and only 59 per cent increase in the polarization capacity of Patient No. 13.

This patient presented clinically a moderate degree of thyrotoxicosis. Nervousness per se appeared to have little effect upon the polarization capacity of the skin. This is in agreement with the observation that the resistance of the body to an alternating current does not change under the influence of emotional reaction (25).

A serious error may occur when the electrode is ill-fitting and is not tightly applied to the skin. It is best to anneal them at frequent intervals. Cases 1, 2, 5 and 7 gave much higher figures for the polarization capacity than for the basal rate. I have no definite explanation for this discrepancy. It is suggestive, however, that Patients Nos. 1, 5 and 7 presented a greater

TABLE I

No.	Name	Age	Sex	Oxygen Per Minute cc.	Heat Production Per 24 Hours Calories	Deviation From Normal	Polarization Capacity Upper Measurement (Microfarads)	Deviation From Normal	Lower Measurement (Microfarads)	Clinical Remarks
1	M. P.	64	F	196	1362	+19	1.66	+100	.89	Toxic adenoma
2	I. B.	32	F	268	1862	+35	1.88	+135	1.1	Toxic adenoma
2A	I. B.	32	F	186	1292	—10	.57	— 24	.29	Seven weeks after removal of adenoma
3	L. B	49	F	242	1682	+28	.77	+ 1	.45	Toxic adenoma
3A	L. B.	49	F	215	1494	+11	.56	— 25	.38	Five weeks after operation
4	R. K.	54	F	254	1765	+20	.59	— 21	.31	Colloid goitre with nervous symptoms
5	M. M.	62	F	283	1966	+48	1.82	+128	1.1	Toxic adenoma
6	A. McM.	52	F	255	1772	+70	1.57	+ 96	1.03	Graves' disease
7	H. H.	44	M	291	2022	+44	1.96	+145	1.3	Masked thyrotoxicosis
7A	H. H.	44	M	237	1647	+14	.96	+ 28	.48	Four weeks after operation
8	M. G.	60	M	258	1793	+42	.98	+ 20	.60	Masked thyrotoxicosis
9	B. M.	33	F	274	1904	+50	1.35	+ 69	.81	Graves' disease
10	F. Th.	29	F	197	1369	— 7	.62	— 17	.34	Thyrodectomy for Graves', six months ago
11	E. W.	50	F	211	1466	+33	1.02	+ 27	.44	Graves' disease, treated with radium
12	M. R.	43	F	335	2230	+65	1.99	+149	.12	Thyrotoxicosis with myxedema of legs
13	W	27	F	300	2084	+95	1.27	+ 59	.82	Graves' disease
14	W.	39	F	238	1654	+33	.56	— 25	.35	Pulmonary tuberculosis
15	G.	18	M	211	1466	— 6	.67	— 19	.35	Pulmonary tuberculosis following influenza
16	J. B.	56	M	228	1570	+ 2	.86	+ 15	.6	Colloid goitre
17	W.	28	F	166	1153	—11	.60	— 25	.35	Exophthalmos; mitral stenosis
18	Z.	22	F	151	1049	—19	.56	— 25	.47	Hypothyroidism
19	A. K.	25	F	190	1320	—12	.67	— 19	.32	Hypothyroidism

TABLE I—Continued

No.	Name	Age	Sex	Oxygen Per Minute cc.	Heat Production Per 24 Hours Calories	Deviation From Normal	Polarization Capacity Upper Measurement (Microfarads)	Deviation From Normal	Lower Measurement (Microfarads)	Clinical Remarks
20	G. Sh.	23	F	151	1049	—10	.57	— 24	.35	Hypothyroidism
21	S. G.	18	F	124	861	—29	.53	— 30	.29	Cretinism
22	M.	32	F	160	1112	—17	.36	— 56	.23	Cretinism
23	R. R.	26	F	171	1188	—17	.64	— 18	.31	Hypothyroidism
24	F. G.	16	F	192	1334	—13	.41	— 45	.3	Hypothyroidism
25	M. M.	55	F	123	854	—38	.43	— 42	.24	Postoperative myxedema
26	S. W.	36	F	197	1369	+10	.68	— 19	.38	Colloid goitre
27	Dr. D.	42	M	198	1376	—17	.60	— 25	.35	Hypothyroidism
28	McG.	51	F	300	2084	+44	.68	— 19	.38	Hypertension
29	J. K.	13	M	224	1556	—30	.43	— 42	.3	Dystrophy adiposo-genitalis
30	R.	47	F	158	1098	—30	.44	— 41	.23	Thyro-ovarian obesity
31	M. S.	15	F	213	1480	—14	.76	+ 1	.44	Constitutional obesity
32	R.	30	F	224	1556	+ 4	.86	+ 15	.31	Constitutional obesity
33	T. B.	38	M	414	2876	+30	.68	— 19	.41	Cerebral obesity
34	I. S.	38	M	245	1702	+ 4	.64	— 18	Not determ., very hairy	Constitutional obesity
35	J. B.	42	F	300	2084	+ 7	.76	+ 1	.33	Cerebral obesity
36	R. F.	20	M	218	1515	— 5	.49	— 48	.34	Hypogonadism

	Forehead	L. Chest	L. Forearm	L. Thigh	L. Lower Leg
I. Dial Reading	5.0	4.0	3.5	3.0	2.7
II. Capacity Standard (microfarad)	0.1	0.1	0.1	0.1	0.1
III. Series Resistance (Ohms)	3,300	3,400	2,900	2,200	2,200
IV. Body Capacitance (Product I and II)	0.50	0.40	0.35	0.30	0.27
V. Equivalent Series Resistance (Product of I and III)	15,500	13,600	10,150	6,600	5,940

degree of thyrotoxicosis than the basal rate would indicate. Indeed Patients Nos. 1 and 5, during their stay in the hospital, yielded subsequent basal rates of plus 87 and plus 100, respectively. Clinically they ran a stormy course. Whether we possess in the polarization capacity determination a method for measuring thyroid activity superior to or on par with the basal metabolic rate can be decided on only by a comparative study of a large series of cases. In Cases Nos. 2, 3 and 7 the polarization capacity and the basal rate were determined before and after the thyroidectomy. The difference in the readings before and after the operation were distinct, suggesting the influence the thyroid gland might exert on the polarization capacity of the skin.

Patient No. 12 presented an interesting complication. This patient, Mrs. M. R., age 43 years, came to the hospital in a state of cardiac decompensation. She was well until about three years before when she felt weak and was short of breath on exertion. She became conscious of palpitation. During the preceding four months she had lost 28 pounds in weight. The main points in her physical examination were an enlargement of the heart in its transverse diameter, particularly to the left; widening of the aorta; auricular fibrillation; pleural effusion at the right base. The lower extremities were swollen. However, the swelling did not pit on pressure. The patient was treated in the conventional way. During her stay in the hospital the symptoms of cardiac decompensation cleared, but the swelling of the legs persisted. Because no mitral lesion could be demonstrated and because of the absence of arteriosclerotic heart disease to account for the auricular fibrillation, a basal metabolic study was made and found to be plus 65. The polarization capacity was 1.99 microfarads, for the upper measurement; the lower measurement was 0.12 microfarads. The lower measurements have been invariably lower than the upper in all readings; however, such an extreme figure could be interpreted on the basis of a myxedematous condition only. A patient with edema of the lower extremities of cardiorenal origin was used as a control. The lower measurement reading in the latter was 0.45 microfarads.

It is a clinical observation that some patients with hyperthyroidism may manifest features of partial hypothyroidism. This combination might be explained by the fact that certain tissues, in this instance, of the lower extremities, failed to fix the thyroxine, even though general hyperthyroidism existed (26). The polarization capacity measurement would ap-

pear to offer a means of determining the coincident existence of partial hypothyroidism in a person suffering from general hyperthyroidism.

The group of hypothyroid patients comprised two cretins, one a case of postoperative myxedema, and six patients presenting various symptoms of thyroid insufficiency as described elsewhere (27).

Both the basal rate and the polarization skin capacity were below the normal; however, the polarization skin capacity figures were perceptibly lower than the basal rate.

Patients 14 and 15 presented symptoms suggestive of either early pulmonary tuberculosis or hyperthyroidism. Patient No. 14 had a basal rate of plus 33 and a polarization capacity of minus 25. This patient, during her stay in the hospital, developed pulmonary hemorrhage. The clinical course in Case No. 15 proved that he suffered from pulmonary tuberculosis. Both the basal rate and the polarization capacity were low.

Patient No. 28 had a basal rate of plus 44 and a minus 19 polarization capacity. An elevated basal metabolic rate is not infrequently noted in patients with essential hypertension. It would be of interest to compare the polarization capacity and the basal rate in a large group of patients with hypertension.

Six out of seven patients with obesity have shown a close parallelism between the basal rate and the polarization capacity. Patient No. 33, with cerebral obesity, had, however, a basal rate of plus 30 and a polarization capacity of minus 19.

The following conclusions may be drawn:

The polarization capacity of the skin appears to be influenced by the thyroid gland; it might, therefore, be employed as another means of determining thyroid activity; it should supplement the basal rate determination. Neither method is entirely free of errors, the results should be interpreted in the light of the clinical symptoms of the patient.

A larger number of cases are to be studied by a uniform technic before any conclusion can be arrived at as to the clinical superiority of each method.

SUMMARY

The polarization capacity of the skin was determined by means of a modified Wheatstone Bridge adapted to simultaneous measurements of capacity and resistance. In a group of 16 healthy adults the polarization capacity of the skin of the upper part of the body varied between 0.75 and 0.8 microfarads; the measurement of the lower part of the body varied from 0.35 to 0.45 microfarads.

In 11 patients with thyrotoxicosis the polarization capacity of the skin of the upper part of the body varied from 0.77 to 1.99 microfarads. The basal metabolic rate varied from plus 19 per cent to plus 95 per cent. There was no apparent parallelism between the basal metabolic rates and the polarization capacity of the skin. In three patients of this group the

polarization capacity of the skin after thyroidectomy was perceptibly lower than before the operation. The basal metabolic rates were likewise reduced after thyroidectomy.

In the group of hypothyroid patients were included two cretins, one case with postoperative myxedema and six patients with various symptoms of thyroid insufficiency. In these patients the polarization capacity of the skin of the upper part of the body varied from 0.36 to 0.67 microfarads. It is suggested that the polarization capacity of the skin might be employed as another means of determining thyroid activity.

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HAZARDS IN THE TREATMENT OF THE ELDERLY DIABETIC WITH A REPORT OF CASES

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ARTERIOSCLEROSIS IN DIABETES

In reviewing the causes of death in diabetes mellitus we find that arteriosclerosis with its various manifestations is now occupying the leading place. Not only has the number of diabetics with arteriosclerosis grown larger, but its death rate has increased. The following questions arise: Is diabetes mellitus predisposing to arteriosclerosis? If so, can it be prevented? Can the death rate of arteriosclerotic diabetics be reduced? Are the diabetics with arteriosclerosis presenting special problems in their treatments?

The frequency of arteriosclerosis in diabetes can be partially explained by the fact that the arteriosclerotic age is the most common for the onset of diabetes. There is undoubtedly a group of patients with extensive arteriosclerosis in whom the development of diabetes can be attributed to sclerosis of the arteries in the pancreas. At the same time there is evidence that diabetes of long duration is accompanied by premature arteriosclerosis.

Peripheral arteriosclerosis has been diagnosed with the aid of the x-rays in patients below forty, and even in children with diabetes of a minimum duration of five years. Albutt (1) noted many instances of thickened arteries in children and in comparatively young adults. Bowen and Koenig (2) found that the poorly controlled diabetic has shown a more marked increase in the degree of arteriosclerosis than the properly treated. Morrison and Bogan (3) have demonstrated calcification of the arteries in increasing amounts with the increase in the duration of the disease. White (4) claims that arteriosclerotic changes occur usually in uncontrolled cases and may develop even within one year. With rare exception, every patient with diabetes of ten years' duration has shown peripheral arteriosclerosis. With the improvement in the treatment of diabetes the number of patients with a duration of their disease over ten years has greatly increased, and thus the increase in the number of arteriosclerotic diabetics. There is hope that with still better control of diabetes and with the use of insulin in the proper cases the development of arteriosclerosis will be postponed. Joslin (5) states that no peripheral sclerosis was found in the diabetic children treated for eight years with insulin.

The treatment of the arteriosclerotic diabetic is full of hazards. Coronary sclerosis and sclerosis of the arteries of the lower extremities with resulting gangrene take a prominent place among the complications in dia-

betes mellitus. A too rigid restriction in the carbohydrates of the diet with its sudden drop in the blood sugar may act injuriously on the arteriosclerotic heart muscle. An overdose of insulin may precipitate angina pectoris, coronary thrombosis, cerebral, retinal, and renal hemorrhages. Hypersecretion of epinephrine has been demonstrated in hypoglycemic shock and suggested as the cause of the vascular accidents. The aim of this paper is to illustrate these dangers with a number of cases, and to outline the methods of its prevention. The mechanism of hypoglycemia and the important part it plays in the complications of diabetes is discussed in detail in another paper, to be published soon.

THE HEART IN THE ELDERLY DIABETIC

The function of the heart depends on the nutrition of the heart muscle. The nutrition may be impaired by a lack in the glucose supply caused by a local or general hypoglycemia or by a disturbance in metabolism, as in diabetes or intoxication. In diabetes the metabolism of the heart muscle may be adjusted to a higher blood sugar level or to a larger use of glucose. Budingen (6) finds that angina pectoris is taking the leading place among the cardiac diseases, characterized by a disturbance in the nutrition and the metabolism of the heart muscle. An overdose of insulin may cause cardiac symptoms in a person with a normal heart. In patients with arteriosclerosis there is often found myocardial degeneration and sclerosis of the coronary vessels. Hypoglycemia caused by a low diet or an overdose of insulin in a patient with arteriosclerosis may result in a serious accident. A low carbohydrate diet may be injurious to an elderly diabetic, even in the presence of an elevated blood sugar. General rules cannot be outlined for the treatment of these cases. Each patient requires individual study. The diet should never be low in carbohydrates. Insulin should be used cautiously in small doses when indicated. Some improve with the elimination of the glycosuria and reduction of the hyperglycemia; others may show signs of aggravation of the cardiac condition with the improvement of the diabetes. These cases need special care in the adjustment of diet and insulin. At times it may become necessary to allow a certain amount of hyperglycemia or even glycosuria in order to avoid further impairment of the cardiac condition. The same patient may react differently at different times.

CASE REPORTS

Case No. 1 (B.I.H. Case No. 13382A). O. W., a man, aged 54, came to the Out Patient Department of the Beth Israel Hospital on August 5, 1930, because of pain in his left leg from the knee down. He gave a history of glycosuria discovered by his family physician three years previously. It was accompanied by polydipsia, polyuria, and gradual loss of weight. On a restricted carbohydrate diet the glycosuria disappeared in one week. He then gradually returned to a normal diet. When he entered the clinic his intake was about 250 grams of carbohydrate, 80 grams protein, and 80 grams fat. The urine showed an orange test for sugar. A blood sugar test was not made. His weight was 142 pounds. He was given a diet of C. 100, P. 80, and F. 80, but his intake was often less than this. The urinary sugar gradually disappeared, and the blood sugars were

on September 9, 1930, 124 mgm. per 100 cc. blood, and on November 25, 1930, 140 mgm. In spite of the fact that his diet was raised to C. 120, P. 80, and F. 130, the patient continued to take a lower carbohydrate diet because of fear of the return of the glycosuria. About six months after he was started on a diet he reported for the first time precordial pain radiating to both arms upon exertion. The attacks were gradually increasing in frequency and severity. The patient was advised of the importance of the carbohydrate in his diet, which was gradually raised to C. 150, P. 80, and F. 100. The anginal attacks since then became rare and of milder character. His blood sugars continued to be within normal limits. They were as follows:

July 21, 1931, at 11:00 A.M.—109 mgm. sugar per 100 cc. blood.
Nov. 3, 1931, at 10:30 A.M.—120 mgm. sugar per 100 cc. blood.
Jan., 1932, at 12:50 P.M.—99 mgm. sugar per 100 cc. blood.
May 24, 1932, at 11:50 A.M.—99 mgm. sugar per 100 cc. blood.

This patient developed anginal pain on a low carbohydrate diet while under our observation. The attacks ceased with the increase in the carbohydrate of the diet. It is interesting that the improvement came without any rise in the blood sugar. It is thus evident that a drop in the blood sugar in an elderly diabetic is harmful only in the presence of a low carbohydrate diet. It is probably due to the lack in nutrition of the heart and low glycogen reserve in the liver. It also illustrates the fact that a blood sugar should always be interpreted with consideration of all factors influencing the metabolism and the condition of the patient.

Case No. 2 (B.I.H. Case No. 8960A). A. G., a woman, aged 45. Admitted December 12, 1929, on the Surgical Service of the Beth Israel Hospital because of profuse leucorrheal discharge. She gave a history of loss of weight, weakness, polyuria, polydipsia, and pruritus vulvae of one year's duration. The urine on admission showed an orange test for sugar, and the fasting blood sugar was 258 mgm. per 100 cc. blood. On a diet of C. 74, P. 60, and F. 90, with 10 units of insulin before each meal, the urine became sugar-free and the fasting blood sugar was 0.151 mgm. per 100 cc. Dilatation and curretage, excision of a cervical polyp and anterior colporrhaphy were performed under spinal anesthesia. She was discharged in good condition on the 13th post-operative day on a diet of C. 74, P. 60, and F. 90, with 15 units of insulin once daily. She was seen in the Diabetic Clinic for the first time on January 7, 1930. On a diet of C. 100, P. 70, and F. 90, her insulin was gradually discontinued. In June, 1930, she was started again on insulin because of sugar in her urine. This time she complained of feeling sick soon after taking the insulin. It was discovered that she was very irregular with her meals. At times she would take the insulin and go without a meal. It was some time before the patient learned to follow instructions. In July, 1931, she complained for the first time of a precordial constriction in her chest with palpitation following a dose of 14 units of insulin. A reduction in two units was sufficient to prevent an attack, but caused a glycosuria and hyperglycemia. With every attempt to get her urine sugar-free by an increase in the insulin, the precordial pain returned. She emphatically refused to divide the insulin into two doses and to try on a higher carbohydrate diet. She was then allowed to go along with a slight glycosuria and hyperglycemia. Since then the anginal attacks have almost completely ceased.

This patient has developed anginal pain for the first time while under treatment with insulin. It is interesting that although at one time she was able to take enough insulin to keep her urine sugar-free and her blood sugar within normal limits without ill effects, she now is not able to do so because of the impending anginal attacks. This is the type of case in which a forced reduction in the blood sugar in the presence of an insufficient amount of carbohydrate in the diet may be disastrous. The heart

muscle is apparently not getting enough nutrition, and is therefore adjusted to a higher blood sugar level.

Case No. 3 (B.I.H. Case No. 17749A). E. S., a woman, aged 63. Admitted to the House of the Beth Israel Hospital on April 21, 1931. Glycosuria had been discovered for the first time six years previously. She was then treated at the Boston City Hospital on a diet with insulin for one week. Two months previous to her admission to the House she developed her first attack of precordial pain radiating to her back on climbing a hill. She was relieved of the following anginal attacks by rest and nitroglycerin tablets. On admission her urine showed an orange test for sugar. The glycosuria disappeared on a diet of C. 75, P. 50, and F. 90, with 5 units of insulin daily. She was discharged on the same diet without insulin. In the Diabetic Clinic her diet was raised to C. 120, P. 70, and F. 80, but she continued to take only about C. 80, P. 60, and F. 80. Her urines were mostly sugar-free, although the blood sugars were elevated. Since May, 1931, she has had only one severe precordial attack. In January, 1932, her urine started to show large amounts of sugar. This frightened the patient and on her own initiative she reduced the carbohydrates in her diet. When she came to the Clinic on February 2 and her urine showed three plus acetone and a brown test for sugar, she was admitted to the House to be adjusted on an insulin regime. She was discharged back to the Clinic on a diet of C. 100, P. 60, and F. 110, with 20-0-20 units of insulin daily. She was allowed to show traces of sugar in the urine and a slightly elevated blood sugar. She continued, however, to fear glycosuria and often ate less than she was ordered. It was impossible to persuade her to take a higher carbohydrate diet. Her anginal attacks returned and were getting more frequent and severe. She was finally induced to follow a diet of C. 110, P. 60, and F. 110, with 20-0-24 units of insulin daily, and to ignore traces of sugar in her urine. Since then she has been almost free of anginal attacks.

This patient had angina pectoris before the insulin treatment was instituted. It illustrates the fact that, when necessary, insulin can be used in this type of case, but with great caution. In this case, as in the one preceding, it was necessary to allow a slight glycosuria and an elevated blood sugar in preference to the danger of anginal attacks.

Case No. 4 (B.I.H. Case No. 15636). E. B., a woman, aged 47. First seen in the Diabetic Clinic at the Beth Israel Hospital on December 11, 1930. She gave a history of diabetes mellitus discovered about 18 years ago. She has been on a diet most of the time since. Five years before this admission she was operated on for a kidney stone at the Deaconess Hospital. She has been taking insulin for several years, lately 8 units once a day. She neglected her diet, however, because of the belief that with insulin she could eat as much as she desired. On admission her fasting blood sugar was 385 mgm. per 100 cc., and the urine showed an orange test for sugar. Physical examination showed premature sclerosis. On a diet of C. 100, P. 90, and F. 100, with 18 units of insulin once daily, her urines became sugar-free and the blood sugar dropped as low as 142 mgm. at 11 A.M. About seven months after she was started on the diet with insulin, she developed her first anginal attack. Her blood sugar a few days after the attack was 93 mgm. at 11 A.M. Since that time she continued to have anginal attacks off and on. The insulin was then divided into two doses. It was noticed that at the time her blood sugars were found normal she had more frequent attacks of anginal pain. Her diet was gradually raised to C. 140, P. 90, and F. 60, with 12-0-10 units of insulin daily. She has been allowed to go with traces of sugar in her urine and a slightly elevated blood sugar. On this regime she has been almost completely free of any precordial discomfort.

This is a case of diabetes mellitus of about 19 years' duration. The patient was on insulin for many years but has been taking unrestricted amounts of carbohydrates and showed large amounts of sugar in the urine. She developed arteriosclerosis but never showed signs of angina pectoris. She developed the first attack of anginal pain when her blood sugar was

brought to normal with diet and insulin. In this case, as in the two previous ones, it was necessary to allow occasional glycosuria and hyperglycemia in order to eliminate the anginal attacks.

DISCUSSION

The deleterious effect of a sudden restriction in diet has been observed by many authors. Strouse, et al. (7), report a case of a women in her late fifties who, for experimental purposes, was put on a low carbohydrate diet. She developed frequent attacks of angina pectoris and paroxysmal auricular fibrillation. A diet of 160 gm. carbohydrates was followed by immediate and complete cessation of the symptoms. Root (8) records at least 4 cases of fatal coronary disease during or just after a lowering of the blood sugar. Death from cardiac infarction occurred in three of Blotner's (9) cases shortly after a rapid fall in blood sugar concentration following the administration of insulin. In a clinical study of 35 fatal cases of diabetes mellitus with coronary artery disease, Blotner (9) found that, although most of the patients entered the hospital for varying complains which were not related to the heart, the chief cause of death in 43 per cent of all the series was directly attributable to the heart. It is probable that too intensive treatment of the diabetes acted deleteriously on the arteriosclerotic hearts.

The effect of insulin, or rather of overdoses of insulin, on the cardiovascular system has been studied in normal individuals by Ernstene and Altschule (10) and in diabetic patients by Lauter and Bauman (11), Wiechman and Koch (12), Budingen (6) (Hetenyi (13) and others. It was found that insulin hypoglycemia is accompanied by an increase in the venous pressure, minute-volume output of the heart, pulse pressure, blood flow and ventricular rate. This means a considerable increase in the amount of cardiac work. An elevation of the arterial blood pressure was found by some and not by others. The discrepancy may be explained by the fact that the blood pressure measurements were taken at different intervals by the various observers. The rise in the blood pressure apparently lasts a short time. Hetenyi (13) believes that insulin may cause spasms of the coronary vessels and thus produce a local hypoglycemia. Wiechman (12) calls attention to the fact that the signs of cardiocirculatory failure do not always develop gradually, but that severe symptoms may appear without warning. Change in the color of the patient with increased pulse rate are to be considered as an ominous sign (a sign of circulatory changes). Strouse, et al. (7) believe that insulin is injurious to the elderly diabetic, even in its usual therapeutic doses.

Electrocardiographic studies on diabetic patients who are taking insulin have been carried out by Wittgerstein and Mendel (14), Middleton and Oatway (15) and many others. All of them found changes in the electrocardiographic tracings, especially in the T-wave direction during the insulin reaction. These changes were only temporary. Schaffer, Brucka,

and Friedlander (16) have shown experimentally that during the toxic effect of insulin on the human heart manifold disturbances in the conductivity and contractility occur. The point of attack may be the nervous system or the muscle itself. Strouse, et al. (7) took tracings before, during, and after the insulin shock, and found that intravenous glucose not only relieved the symptoms but restored the electrocardiogram to its original contours. It is worth mentioning here that Meyer (17) and Handowsky (18) have demonstrated on an isolated animal heart that glucose can cause the coronary arteries to dilate. It would be of interest to know the effect of other hypoglycemias (not caused by insulin) on the cardiovascular system. Such studies have not come to my attention in the literature. It would help to decide how much the changes found in the cardiovascular system are due to the insulin itself and how much to the low blood sugar with its by-effects.

INSULIN AS A CAUSE OF VASCULAR ACCIDENTS

In the studies of the effects of insulin on the cardiovascular system, most of the attention has been given to the effects on the heart; there is very little mention of the vascular sysem. There are in the literature only scattered reports of vascular accidents which are attributed to insulin hypoglycemia. In none of them could an explanation of the phenomenon be found. Insulin is usually recognized as the cause of a vascular accident when the symptoms of the insulin reaction clearly precede the vascular insult. An insulin shock may occur without any premonitory symptoms. It also may be overlooked by the inexperienced observer, especially in the presence of other disease. It is thus possible that some vascular accidents which are precipitated by insulin remain unrecognized. At times it is impossible to decide definitely which started first, the insulin reaction or the vascular insult. At other times we may be confronted with the difficult differential diagnosis between diabetic coma, insulin shock, and cerebral hemorrhage. That insulin may produce spasms of the small blood vessels has been suggested before. It has also been found, as will be described in a later report, that hypoglycemia is accompanied by hypersecretion of epinephrine, which is known as a vasoconstrictor. Wohlwill (19) and Westphal (20) claim that the disturbance in the nutrition of the brain during hypoglycemia is a predisposing factor for a cerebral hemorrhage. Wohlwill (19) found severe changes in the brain cells caused by an overdose of insulin. These changes are probably due to the lack in glucose. Wohlwill attributes it to the alkalosis caused by the insulin. If we add the observations in insulin hypoglycemia of increased heart work and elevation (tension in the blood vessels) of the blood pressure, it will be evident that in a patient with sclerotic vessels the possibility of a rupture of a vessel is to be strongly considered. The following cases will demonstrate this possibility, the difficulty in diagnosis, and its dangers.

CASE REPORTS

Case No. 1 (B.I.H. Case No. 8141-5588). A. R., a woman, aged 50. She was first seen in the Diabetic Clinic of the Beth Israel Hospital in October, 1929, when she gave a history of polydipsia, polyuria, and general pruritus of one year's duration. She had lost 20 pounds in three years. The urine on admission showed an orange test for sugar. The blood sugar was 247 mgm. per 100 cc. blood at 10 A.M. Physical examination showed marked general arteriosclerosis with cardiac hypertrophy and blood pressure of 180/70. The findings were otherwise normal, including the eyegrounds. On a diet of C. 90, P. 60, and F. 70, with 6 units of insulin once daily her urine became sugar-free and the blood sugar was 183 mgm. at 11 A.M. On March 1, 1930, the patient developed acute appendicitis and was operated upon the same day under spinal anesthesia. She had an uneventful recovery and was discharged on a diet of C. 120, P. 70, and F. 100, with 10 units of insulin daily. The blood pressure varied between 160/90 and 140/74. She felt well most of the time. In July, 1930, she had a dizzy spell at about 2 P.M. She also had a lump in her throat and had difficulty with her speech. The blood sugar taken a few days later showed 120 mgm. at 11 A.M. The insulin was then reduced to 6 units. She continued to do well. On August 26, 1931, the patient claims that she took her insulin in a dark room without her glasses and that she might have miscounted the lines on her syringe. She then went shopping, walking a long distance. As a result her dinner was delayed for about 1½ hours. On her way home as she approached her house she suddenly developed a sensation of weakness and inward trembling. She then noticed that her legs, especially the left one, were giving out. She had to be carried up the stairs to her house. Upon examination the same evening she complained of numbness of the entire left side of the body and weakness of the left arm.

An ophthalmoscopic examination revealed two small fresh hemorrhagic spots. The blood pressure was 180/80. The heart was normal. The neurological findings were as follows: ptosis of the right upper lid, coarse nystagmus on looking to the right, and slight nystagmus on looking to the left. There was weakness of both upper and lower left extremities. The knee jerks were decreased and the ankle jerks could not be obtained. There was hypotonicity of the left arm and leg. The plantar flexion was normal. The sensory examination showed a tendency to hypoalgesia on the left, with subjective hyperesthesia on the same side. The left leg was cold and sweaty. The urine was sugar-free. A blood sugar test was not made. A diagnosis of a right cerebral hemorrhage with retinal hemorrhages was made.

I believe that in this case an insulin reaction was the cause of the cerebral and retinal hemorrhages.

Case No. 2 (B.I.H. private case No. 11878). J. G., a man, aged 62. The patient was first seen by me on the evening of August 19, 1931. The history was obtained from his son, since the patient was in a semi-comatose state. He stated that the patient was known to have had hypertension and diabetes for many years and had frequently complained of headaches. He has been on an irregular diet with small doses of insulin for several months. For the last two or three weeks the patient has complained of severe headaches, much more severe than at any previous time. He has had x-ray studies of his sinuses and other examinations, which did not reveal the cause of his headaches. He was put to bed by his family physician because of an elevated temperature (98.8°). An acute pharyngitis and sinusitis was suspected. However, the patient was getting up every day for a few hours. He fell several times, injuring his left knee. His family attributed this to his general weakness. During this episode he omitted his insulin. On examination the patient was found in stupor but responded to some questions, although very slowly. He complained of a severe headache. The breathing was not labored. The pupils were equal and reacted to light. Ophthalmoscopic findings were normal. The tongue was dry and coated. There was an acetone smell from his breath. There was a questionable stiffness of his knee. The heart and lungs showed nothing abnormal. The temperature was 99.6°; pulse, 84; and blood pressure, 180/90. The left knee showed signs of a few small lacerations. The left patella was more freely movable than the right and the quadriceps tendon on the left below the patella was more flaccid than on the right. The left knee jerk could not be obtained. There was no Babinski sign nor ankle clonus. The urine contained large amounts of sugar

and acetone. The blood sugar was 350 mgm. per 100 cc. blood, and there was four plus acetone in the blood.

The patient was able to take nourishment during that day. He was able to urinate when urged. With forced fluids and insulin with carbohydrates his acidosis was cleared by the morning and the urine became sugar-free. The patient, however, was relapsing into a deeper coma. He was then removed to a hospital. A low blood sugar was suspected, hence he was given large amounts of carbohydrate by mouth and intravenously. An hour later the urine again showed sugar and the blood sugar was 311 mgm. The CO_2 combining power was 35 volumes per 100 cc. blood. The patient continued in coma. His left arm and leg seemed to have a weaker response than the right. A lumbar puncture revealed xanthochromic fluid. The spinal fluid pressure could not be measured because of a leak in the apparatus. The total protein was 90, sugar 127 mgm. and chlorides 630 mgm. per 100 cc. The cell count was 7.

Soon after the lumbar puncture the patient started to respond to questions. It was then noticed that he was unable to move his left leg, and that the grip of his left arm was weaker than that of the right. The lumbar puncture was repeated on the following day and the pressure was found to be normal. The headache disappeared the second day. He showed a rapid improvement, although he was somewhat irrational for one week and abnormally facetious for several weeks. The paralysis of the left leg lasted only a few days. The patient was discharged to his home completely recovered five weeks after admission on a diet of C. 140, P. 80, and F. 100, with 8 units of insulin once daily. The urine was sugar-free, and the blood sugar was 121 mgm. at 11 A.M. The insulin was discontinued after a while. The patient is doing well. The discharge diagnosis was diabetic acidosis, subarachnoid hemorrhage, and hemiplegia.

This patient has apparently developed a slowly progressing subarachnoid hemorrhage and hemiplegia. It was complicated by a diabetic acidosis which followed indiscretion in the diet and omission of the insulin. It is possible that a too rapid drop in the blood sugar aggravated the subarachnoid hemorrhage.

This case illustrates the difficulties in the differential diagnosis of diabetic coma, cerebral hemorrhage, and insulin coma. It also shows the great caution needed in the administration of insulin in this type of case.

Case No. 3 (B.I.H. Case No. 9753A). R. S., a woman, aged 45, came to the Out Patient Department at the Beth Israel Hospital on February 4, 1930, because of poor vision. She gave a history of diabetes mellitus of several years' duration (? 10 years). She had been on insulin for about 4 years. She was not following any diet but restricted herself on carbohydrates. She was taking 8-0-6 units of insulin daily. On admission her blood sugar at 11 A.M. showed 96 mgm. per 100 cc. blood. Her eye grounds showed many large and small retinal hemorrhages. She returned on April 29, complaining that her eyesight suddenly became worse two days before. She stated that it followed her insulin, which was given her by a different member of the family than usual. She thought that she received a double dose by mistake. The eyegrounds on that day showed many fresh subretinal and retinal hemorrhages. The vision was very poor. Her blood sugar at 11 A.M. was 95 mgm. per 100 cc. blood.

This patient has developed a progressive hemorrhagic retinitis, while taking insulin without following any definite diet but sharply restricting the carbohydrates. There is a possibility that the last aggravation of the retinitis was brought about by an insulin overdose. It illustrates the dangers of insulin treatment in this type of patient.

DISCUSSION

Transient hemiplegias following an excessive dose of insulin have been reported by Konigshaus (21), Ravid (22), Deicke (23), Miller and Tresher

(24) and a number of others. Traut's (25) patient's right hand and arm were paretic for many weeks after a severe insulin coma. Lauter and Bauman (11) have seen three cerebral accidents 3 to 5 hours after insulin administration. Ehrman and Jacoby (26) reported two autopsies of diabetic coma treated with insulin in whom small and large hemorrhages were found in the brain and in the other organs. Von Grafe (27) in von Noorden's clinic found an aggravation in the hemorrhagic retinitis in patients treated with insulin. Ravid's (22) case has shown under insulin treatment a marked progression of the retinal involvement in the form of numerous small hemorrhages in both fundi. Hematuria during insulin treatment has been observed by Moritz (28), Henderson (29), Thomson (30) Gudeman (31), Lauter and Bauman (11) and others. Two such cases have been seen on the Medical Service of the Beth Israel Hospital. The hematuria was mild and of short duration; it occurred during insulin treatment, without any known cause. Both patients had advanced arteriosclerosis. One had a progressive hemorrhagic retinitis and died later in coma of cerebral hemorrhage in a Providence, R. I., hospital.

Feigenbaum (32) has recently reported an interesting case with unconsciousness, convulsions, paralysis, and psychosis following an insulin reaction and lasting an unusually long time. His patient was only 21 years of age and has weathered the situation. An elderly diabetic, however, may not survive under such circumstances. Feigenbaum's conclusions deserve comment: "A few words regarding the prognosis of an insulin reaction will be in place here. The mild reactions, whether treated or not, always end in the complete disappearance of symptoms. Severe reactions terminate satisfactorily sometimes even without treatment. We can safely say from our experience and from those of others that a reaction which has lasted several days does not point to a fatal outcome. Sporadic deaths have been reported as a result of insulin reactions, but these are of rare occurrence. And the question always arises, in a severe diabetic requiring insulin, whether the death attributed to 'insulin shock' is not due to a complication of diabetes. Perseverance in the administration of glucose intravenously will usually result in recovery from an insulin reaction. Because a reaction is not a serious matter and because it indicates that the maximum effect of insulin has been secured, it should not be regarded with undue apprehension. Just as with digitalis, one must give a quantity sufficient to cause mildly toxic symptoms in order to produce the maximum effect, so one should force the administration of insulin until mild reactions are encountered."

On the ground of the cases presented in this paper and those reported from the literature, as well as on the ground of his own case, I cannot endorse this statement. As long as we find such severe complications with the overdose of insulin, we must strongly advise against the method of "forcing the administration of insulin until mild reactions are encountered." A severe reaction with its after-effects may develop unexpectedly,

as it did in his case. It is unjust to the patient to put him knowingly in such a dangerous position. I feel that precautions must be taken to avoid an insulin reaction and to arrest it as quickly as possible.

SUMMARY AND CONCLUSIONS

There is a noticeable increase in arteriosclerosis among diabetics. It is almost a rule in the uncontrolled diabetics and common in patients treated with high fat diets. There is some evidence that with the use of insulin, better control of the diabetes and higher carbohydrate diets the development of arteriosclerosis will be delayed. It has also been observed that the death rate of diabetics from cardiovascular disease has greatly increased. A sudden and prolonged restriction in the carbohydrates of the diet and overtreatment with insulin are often to be blamed for this. From a study of the literature and on the evidence of several cases that are herein reported the following conclusions are drawn.

1. The treatment of the elderly diabetic presents special problems because of the presence of arteriosclerosis.

2. Restriction in the carbohydrate of the diet should never be too abrupt and should not be continued for too long a period.

3. Insulin should be used preferably in conjunction with an average carbohydrate diet.

4. A diet containing at least 150 grams of carbohydrates should be the aim.

5. Great care should be taken to avoid and to arrest insulin reactions as soon as possible.

6. The possibility of hypoglycemia or an overdose of insulin as the cause of anginal attacks; cardiac infarct; or cerebral, retinal, renal, and other hemorrhages should be constantly kept in mind.

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Book Review

ENDOCRINE MEDICINE. William Engelbach, M.D. Volumes 1, 2, 3 and an Index Volume. Pp. 1795. Charles C. Thomas, Springfield, Illinois. 1932.

In "Endocrine Medicine" Doctor Engelbach has given us the most recent consideration and analysis of the theory and practice of Endocrinology.

The work consists of four volumes. The first volume considers the history of endocrinology and a compact review of its anatomy, physiology and histopathology based upon analyses of the available facts in both laboratory and clinical research.

In the second and third volumes the author analyzes over 2,000 cases personally studied and discusses the infantile, juvenile, adolescent and adult endocrinopathies. These are dealt with under the following groupings: thyroid, hypophyseal, biglandular (thyroid and pituitary), gonadal, parathyroid and thymic disorders. Each section is arranged in three divisions: the first considers the various endocrinopathies of each life period with the interglandular associations; the second deals with the relation of the endocrinopathies to general practice and the specialties including the associated disorders of the non-endocrine system and the third considers the relation of endocrine disorders to public health, including mental retardation, behavior disorders and psychoses.

General discussion is followed by complete case reports, comments and indications for therapy with evaluation of results. Emphasis is placed on the inherent etiology of all the endocrinopathies occurring during infancy and childhood. Engelbach feels that prenatal prevention is more important than early diagnosis and treatment and strongly advises that prophylactic treatment should be instituted during pregnancy toward correcting maternal hypofunction, especially of the thyroid.

Anthropometric measurements and rate of osseous development are stressed as diagnostic criteria and standards of normal annual variations from birth to 20 years of age are offered. Engelbach more than any other one author, deserves credit for placing these aids in diagnosis within the reach of the general practitioner as well as the student of endocrinology.

"Endocrine Medicine" is a credit to both publisher and author and is recommended to the general practitioner as well as to the endocrinologist. The field of this work is aptly stated by Dr. Lewellys Barker in his Foreword: "Compilations of endocrine knowledge have a particular value for the general practitioner, greater, perhaps, than texts dealing with any other special branch, for the doctrine of the internal secretions permeates the whole of modern medicine."—M. B. G.

Abstract Department

The effect of acetylcholine upon the adrenal glands (Die Wirkung von Azetylcholin auf die Nebennieren). Feldberg, W. and B. Minz, Arch. f. exper. Path. u. Pharmakol. **163:** 66. 1931. Abst., Chem. Absts. **26:** 2507.

Acetylcholine (0.5-1 mgm.) injected into atropinized cats, dogs and rabbits increases blood pressure by increasing secretion of adrenaline. This pressure effect is more marked in cats during chloralose narcosis, because chloralose sensitizes the animal to adrenaline. The pressor action of large doses (5-10 mgm.) is due only in small part to adrenaline. Repeated doses of acetylcholine may reduce the adrenaline content of the adrenal glands to half its original value. Its secretory action is due to a direct effect upon the glands, and not to central or sympathetic stimulation. Large doses of acetylcholine cause enophthalmus, irregular pupillary movement, and central and peripheral contractions of striated muscle. It causes periodic apnea in atropinized cats, and when injected into the carotid of dogs. causes more rapid and deeper respirations.

The differential calorigenic action of the liver and adrenals. Griffith, F. R., Jr., and F. E. Emery, Am. J. Physiol. **97:** 527. 1931.

If the liver contributes to the usual calorigenic response following an injection of adrenaline or stimulation of the adrenal glands, it might be supposed to do so as a result of the stimulation of its sympathetic nerve endings and the same response might be expected, unobscured by any other concomitant of the adrenaline reaction, from direct stimulation of its nerves alone. Stimulation of the hepatic nerves does produce a 10-12% increase in oxygen consumption; this increase is quite transient, being over in five to ten minutes in spite of continued stimulation. If one adrenal is now stimulated through its splanchnic nerve the usual calorigenic response of adrenaline follows; i.e., previous "exhaustion" of the liver does not impair the response to adrenaline. If, on the other hand, the adrenal is stimulated first, with the usual calorigenic response, immediate stimulation of the hepatic nerves produces the usual, transient, hepatic increase in metabolism; i.e., the adrenalemia does not seem to have "exhausted" the liver in the same way as does stimulation of its nerves. Or, in other words, the liver does not seem to be involved in the calorigenic response resulting from stimulation of the adrenal gland.—Authors' Abst.

A biological method of assay of the adrenal cortical hormone. Harrop, G. A., J. J. Pfiffner, A. Weinstein and W. W. Swingle, Proc. Soc. Exper. Biol. & Med. **29:** 449. 1932.

Early symptoms of adrenal insufficiency in adrenalectomized dogs are accompanied by a rise in the blood urea and non-protein nitrogen. This fact is made use of in assaying adrenal cortex extracts. A "dog unit" is defined as the minimal daily dose of cortical hormone per kilogram of weight, to maintain normal body weight and normal blood level of non-protein and urea nitrogen, in an adrenalectomized dog for a period of 7 to 10 days.—M. O. L.

Addison's disease treated with suprarenal cortical hormone (Swingle-Pfiffner). Harrop, G. A., Jr., A. Weinstein and A Marlow, J. A. M. A. **98:** 1525. 1932. Abst., A. M. A.

During the past twenty months the authors have had under observation eight patients with Addison's disease, seven women and one man. Four of these patients have died. The other patients, at the present time, are living and are carrying on more or less restricted activities. All the patients are placed on subcutaneous injections of the cortical extract. Twice a day, a dose of 1 or 2 cc. is given, depending on the apparent severity of the case and the clinical effect. It is possible that certain severe cases will require more. The injections are usually made by the patients themselves, similar to the manner in which insulin is used by diabetic patients. Intravenous injections have been frequently resorted to in an emergency. These have been avoided in general because of the possible excretion of the hormone through the urine, thus resulting in some loss of effect. The material is painless when injected and appears to keep its potency for a period of at least two or three weeks without preserva-

tives. It is kept on ice in the dark, being warmed up only for the injections. Certain general principles in the management of the patient should not be neglected. The patient should be warned against undue physical exertion and on the necessity of proper periods of rest and the avoidance of infections. The constantly recurring anorexia makes the dietary problem a serious one. During relapses it is of importance to administer the cortical hormone in large doses as early as possible. As much as 30 cc. has been administered intravenously at a dose, but such large amounts are rarely needed. These relapses often come on insidiously, and due heed must be paid to complaints of weakness, anorexia or nausea. There is no effect within several hours on any of the commonly studied chemical constituents of the blood, including the serum base, lactic acid or potassium, after injection of the cortical extract, either in normal persons or in patients with Addison's disease. Together with the use of the extract carbohydrates should be given by mouth in as large amounts as may be tolerated, and use should be made of dextrose and salt infusions subcutaneously or intravenously when indicated. Such infusions of fluid by vein must be given slowly and with great care. Hypoglycemia should be vigorously combated, and frequent blood sugar studies are advisable to control the efficacy of treatment. The authors have recently used continuous intravenous dextrose injection, by the technic of Warthen, with success in the treatment of an abrupt and severe relapse. By this method, not only is a continuous supply of dextrose furnished and hypoglycemia absolutely prevented, but a free excretion of urine occurs at all times. Drugs, such as epinephrine or pituitary solution (ampules of pitressin), for raising the blood pressure may also be given in minute constant amounts in the injection fluid. Their efficacy has not yet been demonstrated. Just as in the case of the experimental animal, these patients are apt to become very cold and require external warmth. All the various suprarenal gland preparations are essentially useless, and large injections of epinephrine should be avoided except in definite circulatory collapse and as an emergency measure only. When administered by mouth in many patients, epinephrine tends to aggravate nausea, if this is already present.

Lowered resistance to heat in adrenal insufficiency. Hartman, F. A., J. E. Lockwood and L. M. Lockie, Proc. Soc. Exper. Biol. & Med. **29**: 409. 1932.

Adrenalectomized rats are more affected by environmental temperature of 37 to 40° C. than are normals, and easily pass into convulsions and die in such heat. Cortical extract is able to protect adrenalectomized animals considerably. After exposure to a temperature of 38° C. for 78 to 110 minutes, normal rats had the lowest tissue water content, adrenalectomized rats the highest and cortin treated adrenalectomized animals an intermediate amount. The greatest differences were in the skin tissues. It is suggested that less effective mobilization of water is in part responsible for the lowered resistance to heat in adrenal insufficiency.—M. O. L.

Protection of adrenalectomized animals against bacterial intoxication by an extract of the adrenal cortex. Hartman, F. A. and W. J. M. Scott, J. Exper. Med. **55**: 63. 1932.

Young male albino rats were adrenalectomized. Sixteen were injected twice daily with cortin while an equal number were injected with the same volumes of isotonic sodium chloride solution. Two weeks after adrenalectomy, the cortin injected rats had a higher resistance to typhoid vaccine as shown by the symptoms and survival in the two series. All saline injected animals died while 10 cortin injected animals survived. In the second experiment it was shown that cortin protected adrenalectomized rats against dead staphylococci injected daily in increasing amounts. On the eighth day half of the sodium chloride injected animals had died, while all of those injected with cortin survived. During the height of bacterial intoxication, relatively large amounts of cortin seemed to be required.—F. A. Hartman.

Acute insufficiency of the adrenals four years after birth trauma (Akute Nebenniereninsuffizienz 4 Jahre nach Geburtstrauma). Hepner, F., Arch. f. Kinderh. **90**: 10. 1930.

A female child, born after difficult labor during which one femur was fractured, had sudden onset of abdominal pains and high temperature at the age of four. No symptoms of any kind had been observed before that time. Convulsions developed later on. The child was brought to the hospital on the third

day with a temperature of 40° C., with slightly increased rate of respiration and a pulse rate of 164. The heart sounds were clear. Physical examination and x-ray showed a circumscribed pneumonic lesion on the left side. The abdomen was normal. There was some vomiting of coffee-ground material. The child died in coma on the 4th day of illness. Autopsy revealed bilateral calcification and ossification of the adrenals with complete destruction of the medullary substance due to an old hemorrhage. The adrenal cortex showed nodular regeneration. There was evidence of some enteritis. It is assumed that the child succumbed to the mild intestinal infection on account of adrenal insufficiency in spite of the presence of nodular cortical tissue. This would point to the importance of medullary function in the maintenance of body resistance. The discussion is supported by ample quotations from the literature.
—M. A. Goldzieher.

Animal experiments and clinical experience with the adrenal cortex hormone (Tierexperimentelle und klinische Erfahrungen uber Nebennierenrindenhormone). Loewe, S., L. Marx, F. Rothschild, and H. E. Voss, Klin. Wchnschr. **11**: 281. 1932.

Extracts of the adrenal cortex were tested on female rats to determine the effect on virilism as measured by the development of the rudimentary prostate. Large doses of the more refined extracts caused development in 50% of the cases. The method of preparation of the extract and the quantity administered is not stated. The substitution function of the extracts was tested on adrenalectomized cats with positive results. Three cases of Addison's disease were treated with unquestionable improvement. The patients were observed for a few months. In one case the effect of the extract on the blood sugar level was carefully followed.—J. E. Lockwood.

The effect of bilateral suprarenalectomy in adult albino rats on the natural and acquired resistance to Bartonella muris anemia. Marmorston-Gottesman, J. and D. Perla, J. Exper. Med. **55**: 109. 1932.

Normal adult albino rats of non-carrier stock possess a high degree of natural resistance to spontaneous infection with Bartonella muris anemia, but may be readily infected by the injection of whole blood of an anemic splenectomized rat. Though the morbidity of the disease under these conditions is high, the mortality is extremely low. The removal of the spleen in rats of non-carrier stock causes a marked increase in the susceptibility to spontaneous infection with Bartonella muris, but the mortality is considerably lower than in suprarenalectomized rats of non-carrier stock similarly infected. Suprarenalectomized rats of non-carrier stock injected with large amounts of blood of anemic rats are killed by toxemia of the infection before the anemia becomes severe. The nature of the rôle of the suprarenal gland in natural resistance to this infection is of a general character. There is no change in the type of tissue reaction following infection in suprarenalectomized rats but an increased susceptibility to toxic substances produced in the course of a first infection. The acquired resistance to Bartonella muris is unaffected by subsequent suprarenalectomy. This procedure in the rat does not alter the acquired resistance to Trypanosoma lewisi established by a first infection. Suprarenalectomy does not influence the acquired resistance to typhoid vaccine. These observations indicate that once a cellular or humoral immunity is established to an infection or an antigenic substance, this acquired resistance cannot be broken down by subsequent suprarenalectomy. The mechanisms of acquired and natural resistance are dependent on different physiological processes in the organism and are not merely quantitative variations of the same process as is generally assumed.
—D. Perla.

The difference between the action of adrenine on the glycogen of the liver and that of the muscle (Action différente de l'adrénaline sur le glycogène du foie et sur celui des muscles). Nitzescu, I. and N. Munteanu, Compt. rend. Soc. de biol. **108**: 294. 1931.

Six dogs were injected with adrenine at various points in the vascular system. The blood in the hepatic veins contained more sugar than that in the portal. The lactic acid content was greatest in blood leaving the muscles and least in that leaving the liver. The hyperglycemia following adrenine injection is due, therefore, to mobilization of glycogen by the liver, while the simultaneous increase in lactic acid is due to mobilization of glycogen in the muscles.
—J. C. D.

The sensitization of vascular response to "sympathin" by cocaine and the quantitation of "sympathin" in terms of adrenalin. Rosenblueth, A. and T. Schlossberg, Am. J. Physiol. **97:** 365. 1931.

In experiments on cats the action of sodium bicarbonate, glygocoll, calcium chloride and cocaine on the rises in blood pressure produced by injections of adrenaline in Elliott's preparation was studied. Cocaine proved to be the only effective sensitizer among these substances. Cocaine was more toxic to animals deprived of their adrenal glands than to animals with these glands present. It did not increase the effectiveness of adrenaline in accelerating the heart, but it did sensitize smooth muscle to the action of adrenaline. There is a close similarity between the action of cocaine as a sensitizer of smooth muscle to the influence of adrenaline and its rôle as sensitizer to the action of sympathin. This evidence favors the view of the identity of adrenine and sympathin.
—Authors' Summary.

Suprarenals and blood pressure (Nebennieren und Blutdruck). Rusznyak, S., Deutschr. med. Wchnschr. **58:** 573. 1932.

Szent-Györgyi has shown that adrenaline is a less potent modification of a substance, which he names novadrenaline. Novadrenaline is 10-20 times more potent. Subcutaneous injection of 0.1 mgm. raised the blood pressure from 120 mm. Hg. to 180 mm. Hg. for 30 minutes and there was also a rise in blood sugar.—E. Kodicek.

Does adrenaline influence the entrance and exit of lactic acid ions in the muscle (Beeinflusst Adrenalin den Ein- und Austritt von Milchsaureionen aus den Muskeln)? Wesselkina, W. M., Ztschr. f. d. ges. exper. Med. **79:** 630. 1931.

Since the adrenaline output is increased in muscular activity and the muscle glycogen depleted under the influence of adrenaline, adrenaline might influence the lactic acid production in muscle. The excised gastrocnemius of the frog was placed in oxygenated Ringer's or Tyrode's solution containing adrenaline or adrenaline and sodium lactate. From the estimation of the lactate concentration of the bath after various intervals of time, the following conclusioins were drawn: Adrenaline increases the lactic acid output from the resting muscle and decreases the entrance of the same into the muscle; adrenaline increases the lactic acid content of muscle, which is in agreement with the findings of Cori and Cori on the breakdown of glycogen in the presence of adrenaline; there is no evidence of a change in the permeability of the muscle fibre for lactic acid ions, the exit and entrance of which is dependent upon the laws of diffusion only; the exchange of lactic acid between blood and non-participating muscles must depend chiefly on its exchange between the blood and the tissue fluid.—F. H. Pratt.

Studies on suprarenal insufficiency. X. Depressor responses to small doses of adrenalin in the rat, induced by loss of the suprarenal medulla. Wyman, L. C. and Caroline tum Suden, Am. J. Physiol. **101:** 282. 1932.

In urethanized and in unanesthetized normal rats minimal effective intravenous doses of adrenaline produced only pressor responses. In etherized normal rats similar minimal doses occasionally produced depressor effects. In suprarenalectomized rats having transplants of cortical tissue but no demonstrable chromaffin tissue (either urethanized, etherized or unanesthetized), small doses of adrenaline produced depressor responses, larger doses produced pressor-depressor responses and much larger doses were required to produce purely pressor effects. In suprarenalectomized rats similar results were obtained unless the blood pressure was low, when pressor responses alone were seen. Removal or simple ligation of both suprarenal glands was immediately followed by reversal from pressor to depressor of the vascular responses to small doses of adrenaline. The reactions to increasing doses were the same as those in transplanted rats. No significant changes in heart rate were observed. Microscopic observation of blood vessels during the injection of adrenaline in normal and in transplanted rats showed only constriction of the ear vessels, predominating constriction of the intestinal vessels in normals, and brief constriction followed by marked dilatation of intestinal vessels in transplants.
—Authors' Summary.

The endocrine glands and molting in Triturus viridescens. Adams, A. Elizabeth, Alberta Kuder and Leah Richards, J. Exper. Zool. **63**: (No. 1.) 1932.

After thyroidectomy or hypophysectomy or a combination of the two, molting is inhibited in Triturus viridescens and the animal becomes blackened by the accumulation of unshed cornified layers of the epidermis. The uncornified layers also increase in number and a semi-cornified region appears between them and the cornified ones. A molt can be induced after any of the above operations by administering thyroid hormone (either by grafts or thyroxine) or by insertion of iodine crystals. Pituitary grafts (pars anterior or whole gland) are only effective in hypophysectomized or incompletely thyroidectomized animals. Histological study of the thyroids of hypophysectomized animals indicates that the activity of the glands is reduced. Grafts of pars anterior into these animals stimulate the thyroid to release its stored secretion. It is probable that the condition of the skin and its periodic molting in Triturus are under the control of a pituitary-thyroid mechanism. Apparently the thyroid stores the essential chemical substance iodine that is needed in regulating metabolism, but its release is under the control of the anterior lobe of the pituitary.—Authors' Abst.

Myopathic family, with hypertrophic, pseudohypertrophic, atrophic and terminal (distal in upper extremities) stages. Barnes, S., Brain, **55**: 1. 1932. Abst., J. A. M. A., **99**: 176.

Barnes describes a variant of myopathy, occurring in many members of a single family, which passed through four phases—hypertrophic, pseudohypertrophic, atrophic and terminal—the last stage being associated with a distal atrophy of the upper extremities. Other clinical characteristics were early loss of tendon reflexes, late onset and slow progress, an almost constant association with adipositas universalis, and a relative absence of abortive forms and of polymorphism. The author states that a large and increasing body of evidence is available, which goes to prove that myopathy (muscular dystrophy) is determined at the birth of the ovum and is derived as a factor or as factors inherited from one or both of the two gametes which form the zygote. In rare cases, a new mutation (variation in a normal gene) may arise and be the cause of the condition in the individual developed from that zygote and be transmitted to his descendants. As to whether the effects of the mutant are manifested directly during the development of the individual, or indirectly through the endocrine glands, has not been established. The frequent association of myopathy with adiposity and other evidence of endocrine imbalance may be interpreted on strictly genetic lines, the hormone disturbance being a secondary effect of the mutant. In those cases in which microbic disease, trauma, overwork, and so on, are antecedent in the history, they are merely factors which determine the onset or accelerate the progress of the disease in an individual who is a potential myopathic, i.e., a genotype carrying the mutant gene or genes. Apart from the presence of such underlying factors, it is probable that the muscular dystrophy can never arise.

The frequency of mongoloid imbecility; the question of race and apparent influence of sex. Bleyer, A., Am. J. Dis. Child. **44**: 503. 1932.

Mongolian imbeciles were one-fourth of 1% of the entire enrollment (approximately 50,000) of children in a dispensary in 14 years and 14.6% of those mentally defective. Males predominated. The Bureau of Census in this country reports 153 mongolian imbeciles per 100,000 of population. On the basis of 14.6%, this would indicate that there were 28,000 mongolian imbeciles in the United States at this time. The condition has been found to be present in 31 races. The author has knowledge of 8 negroes contradicting the views of Cruikshank that this race did not show this type of imbecility.—M. B. G.

Individual variation in serum calcium in normal men and women. Boynton, Ruth E. and Esther M. Greisheimer, Proc. Soc. Exper. Biol. & Med. **28**: 907. 1931.

From a determination of serum calcium on 17 women and 11 men at triweekly periods for 4 weeks, the following was found: (1) The serum calcium level for women was definitely lower than for men. (2) There was a greater daily variation in the serum calcium for women than for men, as well as a greater absolute range in calcium levels. (3) There was a tendency for the

serum calcium to be highest in the pre-menstrual period and lowest in the menstrual period. This was evident in the mean serum calcium values for each week in the menstrual cycle. The fact that in 12 of 17 individuals, the lowest weekly mean serum calcium occurred in the menstrual or post-menstrual period further substantiates the finding that there is a fall in blood calcium following menstruation. (4) In women there seems to be a regular cyclic curve of blood calcium level which is not present in men.—Authors' Summary.

Glycemia in cachexia of nurslings. Jaso, E., Am. J. Dis. Child. **43**: 1061. 1932.

The study of lesions of endocrine glands may throw some light on the nature of the hypoglycemia in athreptic children. In the pancreas in athreptic children Mattei found an increase in the islands of Langerhans and signs of hyperactivity. In the suprarenal glands there were lesions in the medulla with diminution in the volume and weight of the entire gland. The thyroid showed atrophy and degeneration. The logical sequence in athrepsia should be hypoglycemia as the result of hyperinsulinemia not corrected by the hyperglycemic reflex due to the discharge of epinephrine. The practical conclusion from this consideration is that the treatment of athreptic infants with injections of insulin is illogical and not without danger. The success attributed to insulin is due exclusively to the administration of carbohydrates that necessarily follows it.
—M. B. G.

Experiments on the effect of hormones on the "yellow cells" of the intestine (Versuche zur Beinflussung der "gelben Zellen" des Darmes durch Hormone). Kahlav, G., Ztschr. f. d. ges. exper. Med. **80**: 190. 1932.

Beneath the glandular epithelium of the mucosa of the stomach and intestine, especially in the fundic portion of the gland ducts there are in man and many animals, cells which contain definite granules. These cells are flask-shaped with their bases toward the periphery, the tip toward the lumen. In unstained preparations these granules are yellow, therefore Schmidt has called these cells "yellow cells." Because of their staining properties, they have been called "chromaffin cells" (argentaffine cells or cells of Heidenhain). These cells were studied in the guinea pig. The duodenum contains the greatest number, the jejunum and the stomach next and about the same, then the colon and appendix. The number is variable in different individuals. In series of both "acute" and "chronic" experiments, guinea pigs were given insulin, thyroid extract, and an hypophysis extract (Tonephin). All of these extracts caused an increase in the number of yellow cells. Insulin produced the least and "Tonephin" the greatest effect. The increase in the number of cells was also greater in the "chronic" than in the "acute" experiments. The author suggests that these cells may belong to the endocrine system and points out the possibility that they may be an expression of an increased or decreased activity of the intestine.—A. C. Ivy.

Diagnosis of pluriglandular diseases (Zur Diagnose: "Pluriglandäre Erkrankung"). Maas, O., Endokrinologie, **7**: 262. 1930.

A description is given of two cases diagnosed as pluriglandular.—B. C.

Specific hematopoietic hormone in normal gastric juice. Morris, R. S., L. Schiff, G. Burger and J. E. Sherman, J. A. M. A., **98**: 1080. 1931. Abst., A. M. A.

It occurred to the authors that the unknown factor, which Castle demonstrated to be absent in the gastric juice of pernicious anemia, might be effective when given intramuscularly or intravenously, though he had shown that it was inert when given by mouth in the amounts contained in 300 cc. of normal gastric juice daily for ten days. By experiment, first on animals and later on man, they found that normal gastric juice, after neutralization, may be injected intramuscularly without undue local or general reaction. They gave a few doses intravenously but abandoned this method for the present, because of the reactions that occurred in some cases. Gastric juice for their experiments was obtained from the fasting stomachs of individuals free from anemia. After preliminary lavage, subcutaneous injection of histamine was given and the resulting secretion collected. The intramuscular injection of from 10 to 20 cc. of normal gastric juice gives a reticulocyte response so slight as to be negligible. Next an attempt was made to concentrate the gastric juice. Vacuum distillation yielded a highly potent product. Intramuscular injection of this

material was followed by a remarkable, almost immediate, reticulocyte response. Ten hours after the first injection of a concentrate obtained from 450 cc. of normal gastric juice the reticulocytes rose from 0.5% to 5% and there was striking polychromatophilia. There was also a rise in the total white cell count with a marked increase in the percentage of neutrophils. At the end of thirty-six hours the reticulocytes amounted to 17.6%. The total red cell count at this time was 2,100,000. There were, therefore, approximately 369,000 reticulocytes per cubic millimeter. Coincident with the rise in the reticulocytes, there was a marked increase in the number of red cells containing nuclear particles or Howell-Jolly bodies. For the hematopoietic hormone which they have demonstrated in normal human gastric juice, the authors have proposed the name addisin, after Thomas Addison, who first described pernicious anemia.

Acid-base equilibrium of blood in pathological conditions; changes observed in toxemias of pregnancy. Muntwyler, E., N. Limbach, A. H. Bill and V. C. Myers, J. Biol. Chem. **90**: 607. 1931.

An acid-base equilibrium study of the plasma of 26 cases of toxemia of pregnancy is reported. A lowering of the alkaline reserve (to an average of 20.9 mm. of plasma bicarbonate concentration) was found, as has been observed in normal pregnancy. The pH was elevated to 7.48 or above in 13 of the 23 cases studied ante partum, with an average pH of 7.47. The total base concentration was decreased from the average normal of 153.8 mm., as given by Card and Peters, to 144.7 mm. (uncorrected for loss due to phosphorus). Post partum the findings showed on the average a considerable increase in the bicarbonate and total base, with a slightly smaller increase in total acid and a slight increase in protein and pH. There was a small decrease in chloride. The lowered plasma bicarbonate (so-called acidosis of pregnancy) was not due to an accumulation of abnormal acids. From the data at hand it would seem most logical to conclude that the fall in the plasma bicarbonate noted in the present series of cases of toxemia of pregnancy (and in normal pregnancy) is due to hyperventilation, and that the fall in total base is a further compensatory phenomenon.—Authors' Summary.

Histamine as the hormone for gastric secretion. Sacks, J., A. C. Ivy, J. P. Burgess and J. E. Vandolah, Am. J. Physiol. **101**: 331. 1932.

Histamine has been isolated from acid extracts of the pyloric mucosa as a sulphate and picrate. The method is described. Vaso-depressor and secretory assays on all fractions from the original acid extract to the final product of histamine crystals and mother liquor yield strong, if not conclusive, evidence that histamine is the sole secretory excitant active subcutaneously in acid extracts of the pyloric mucosa and that histamine was not produced by the chemical procedures employed. Histamine (0.5-1.0 mgm.), pilocarpine (5-10 mgm.) and iso-pilocarpine (10 mgm.) are the only imidazoles out of 10 tried that stimulate gastric secretion. Methylene histamine (5-10 mgm.) does not stimulate gastric secretion. A threshold dose of a gastric secretory excitant is present in 1 or more liters of urine which is to be expected on the basis of the histamine content of urine. Histaminase destroys the gastric secretory effectiveness of "gastrin" solutions. Histamine adsorbed to Lloyd's reagent maintains its vaso-depressor and secretory properties. —Authors' Summary.

Histo-physiogenesis of the glands of internal secretion—thyroid, adrenal, parathyroid, and thymus of the chick. Sun, T. P., Physiol. Zoöl. **5**: (No. 3). 1932.

Freshly laid Leghorn eggs were incubated. The morphology of the thyroid, parathyroid, adrenal, and thymus glands from the very beginning of incubation to the hatching period was observed. The iodine content of the thyroid glands and the epinephrine content of the adrenals at twenty-four-hour intervals from nine and one-half days of incubation to the hatching period were determined. The following conclusions were drawn: The active principle of the thyroid glands in the embryo increases in both the absolute and relative amount, the latter indicating that the growth of the active principle is greater than that of the gland tissue. The epinephrine content of the adrenal glands increases in both absolute and relative amount. The increase of relative

amount determines the degree of increase in the cortical and medullary tissue per unit weight of gland. There seems to be an interrelation or reciprocal relation between the thyroid and adrenal glands. The percentage of active principles of the gland tissue of both the thyroid and adrenal glands reaches a normal level immediately after hatching.—Author's Abst.

Histo-physiological study of the glands of internal secretion and their effect on ossification in the chondrodystrophic and "Sticky Chicken" embryo. Sun, T. P., Physiol. Zoöl. **5**: (No. 3). 1932.

Thyroid, parathyroid, adrenal, and thymus glands were examined microscopically at 17 days of incubation and iodine content of thyroids, epinephrine content of adrenals, and bone compositions were chemically determined. The results obtained from deformed chicken embryos were compared with those found in both Leghorns and normals from the same lot of eggs that furnished the deformed chicks. The fact that deficiency of thyroid secretion is followed by disturbance in metabolism was established. The significant results in deformed animals were: (1) The thyroid, adrenal, and thymus were smaller; the parathyroids, enlarged; all showed a pathological condition. (2) No striking changes in the microscopic structure of thyroid and adrenal associated with the changes of gland size could be detected. The thymus showed a degenerated or undeveloped condition. In sections of the parathyroid, cells of the peripheral region were elongated and the cytoplasm failed to stain. (3) The iodine content of the thyroid was undetectable. The epinephrine determination showed that growth of the adrenal cortex was retarded more than in the medulla. (4) The metabolism of Ca, P, and organic matter of the bones was distorted. The degree of deficiency of phosphorus is greater than that of calcium. The percentage of water content of the bones is lower than that of normals.
—Author's Abst.

The effects of hormones and certain other substances on cell (luminous bacteria) respiration. Taylor, G. W., J. Cell. & Comp. Physiol. **1**: 297. 1932.

Evidence is offered to show that luminous bacteria afford a very rapid and easy method of measuring the rate of oxygen consumption sufficiently accurate for most purposes. Using this method, it was found that increases in the amount of nutrient material (glycerine, glucose, and peptone) caused a marked increase in the respiratory rate. Methylene blue accelerated the respiratory rate (95%) while m/10,000 KCN decreased the rate 92%. The ovarian hormone, theelin, epinephrine, pitocin, and pitressin had an acceleration effect when present in concentrations so low as to be of no nutrient value. The hormones from the thyroid, parathyroid, liver, and pancreas were less effective in accelerating respiration than an equivalent amount of peptone. Cresol had an initial inhibitory effect, but is rapidly detoxicated by the bacteria and is then apparently of some nutrient value. The suggestion is made that adrenaline exerts its effect through one of the oxyadrenalines acting as a hydrogen acceptor. The intensity of luminescence is to a great extent independent of the rate of respiration, but not entirely so. Nutrient material is essential for the maintenance of a constant intensity of luminescence. Adrenaline was the only hormone to exert a marked effect on the luminescence and it always caused a decrease in intensity.—Author's Abst.

The influence of the function of the glands of internal secretion on the sugar-secretion-threshold (Über den Einfluss der Funktion der endokrinen Drüsen auf die Zuckerausscheidungsschwelle). Yokota, S., J. Biochem. **15**: 65. 1932.

Experiments were made on rabbits to determine the correlation between the function of the glands of internal secretion and the sugar-secretion-threshold. The suprarenal glands, thyroid gland and the pituitary body were tested. It appeared that hyperfunction of the suprarenal cortex and of the anterior lobe of the pituitary body produces a lowering of the threshold. Hyperfunction of the suprarenal medulla, of the thyroid gland and of the posterior lobe of the pituitary body increases the threshold-value. Hypofunction or afunction of the suprarenal cortex raised the threshold. Hypofunction or afunction of the suprarenal medulla and of the thyroid gland lowers the threshold.—Author's Abst., abbreviated. Tr. by G. L. Banay.

Physiology of the corpus luteum; interrelationship of oestrin and the corpus luteum as determined by their effects in the adult rabbit. Allen, W. M., Am. J. Physiol. **100**: 650. 1932.

It was shown that active progestin-containing extracts of the corpus luteum lose their ability to produce progestational proliferation in the castrated rabbit's uterus when they are given simultaneously with oestrin; 675 r.u. of oeostrin completely inhibit 3 rabbit units of progestin. Large doses of oestrin (1000 r.u.) given during the first 5 days after mating prevent the development of proliferation of the endometrium but do not prevent the development of normal appearing corpora lutea. Similar doses (1000 r.u.) given during the second five days after mating cause extensive endometrial degeneration with sloughing of the endometrium, but they produce no demonstrable changes in the corpora lutea. Under these conditions the placentae start to form but they are very abnormal.—Author's Abst.

The treatment of migraine with emmenin. A preliminary report. Blakie, N. H. and J. C. Hossack, Canad. M. A. J. **27**: 45. 1932.

Struck by the frequency with which migraine is influenced by changes in the functional state of the ovaries the authors administered emmenin, the ovary-stimulating derivative of the placenta, in the hope that through its influence on the ovaries the disease might be ameliorated. In the 20 cases reported the results had been excellent, giving relief to the point of complete freedom from attacks. In addition there were noted improvement of mental functions, loss of excessive weight and a sense of well-being. Further work is planned to define indications and dosage.—R. G. H.

Chromatophore reaction to an oestrogenic hormone. Carroll, P. L., Proc. Soc. Exper. Biol. & Med. **28**: 874. 1931.

The oestrogenic hormone (theelin) apparently has an effect upon the pigmentary system of the tadpole causing albinism. The chromatophore reaction involves a centripetal movement of pigment in the epidermal melanophores and a pseudopodial expansion of the leucophores. The velocity of the reaction is directly related to the concentration of the hormone and the duration of exposure. Intraperitoneal injection causes a more rapid response. It is generally admitted that the pigmentary system of amphibia is controlled by the secretions of the pituitary. Extracts from the pituitary gland cause melanism. The oestrogenic hormone causes albinism. It is probable that in the control of the melanophores and the leucophores there exists a physiological antagonism between the secretions of the pituitary and the oestrogenic hormone.
—Author's Summary.

Precocious menstruation. Craven, J. D., Am. J. Dis. Child. **43**: 937. 1932.

Report of a well-developed girl of 5 years of age who gave a history of vaginal bleeding since birth, occurring with monthly regularity from the age of 3 months to 1 year and then at longer intervals from then on up to the time of reporting. The breasts were enlarged but there was no abnormal growth or distribution of hair. Intelligence was normal. An exploratory laporotomy revealed normal sized adrenals, adult sized uterus and ovaries. Histological examination of the latter showed normal findings. Because of the normal adrenals and negative ovarian findings, the author attributes the prematurity in menstruation to be due to hyperactivity of the sex hormone of the anterior lobe of the pituitary. The sella turcica was normal on roentgenographic examination. The child was sterilized.—M. B. G.

The bio-assay of theelol. Curtis, J. M. and E. A. Doisy, J. Biol. Chem. **91**: 647. 1931.

The assay of theelol in adult spayed rats, subcutaneous injection, shows about 1,500 R. U. per mgm. It is ⅓ to ½ as active when given orally. The injection into 18-day-old rats gives a value of 6,000 R. U. per mgm. It is half as active by enteral administration. By the adult animal technic theelin is twice as active as theelol but by the immature animal method theelin is only one-sixth as active as theelol.—J. M. Curtis.

Studies on the physiology of pregnancy (Beiträge zur Physiologie der Gravidität). von Fekete, K., Endokrinologie, **7**: 364. 1930.

Serum from pregnant individuals loses its power to cause gravid-uterus contraction. It also possesses an antihyphophysis factor, which gradually decreases in late pregnancy. The serum thus provides undisturbed conditions for the gravid uterus. Presumably labor is initiated by the loss of the anti-hypophysis factor.—B. C.

Premature sexual development in children due to malignant ovarian tumors, with special reference to hormonal studies and after treatment. Frank, R. T., Am. J. Dis. Child. **43**: 942. 1932.

Not every tumor of the ovaries in children, irrespective of whether it is malignant or benign, produces pubertas praecox. Three cases are reported, a teratoma producing prematurity, carcinoma without prematurity and embryonal alveolar carcinoma with precocious puberty. The female sex hormone was found in the ovaries of the last patient and post-operatively for one week in the urine of the first two cases. Post-operative roentgen therapy is indicated in the after-care to avoid recurrence irrespective of whether eunuchoidism develops or not. In the case of abdominal tumor in children, the female sex hormone test performed on the urine helps in localizing the origin.—M. B. G.

Hormone of corpus luteum (Etudes sur une hormone du corps jaune). de Fremery, P., A. Luchs and M. Tausk, Arch. néerl. de physiol. **16**: 290. 1931. Abst., Physiol. Absts. **17**: 62.

Extracts were made from cow's and sow's corpora lutea. The hormone was not found in urine of pregnancy nor in placenta; it is soluble in 70 to 96% alcohol, ether, acetone, benzol, and water; it is insoluble in petroleum ether; it is stable to N/100 NaOH of HCl, and on storage in arachis oil. Spayed and virgin rabbits were not suitable for tests, the latter since corpora lutea might appear in the ovaries following the injections. Immature rabbits were therefore used; they were prepared by 8 injections of 10 M.U. menformon and the extract of corpus luteum injected twice daily for 5 days; 1 unit is the minimum amount producing complete transformation of the uterine mucosa into the condition seen in pseudo-pregnancy. The histological changes were only roughly parallel to the decrease in sensitiveness of the isolated uterus to pituitrin. The purest preparation contained ⅛ rabbit unit (as well as ⅜ mouse unit menformon) per mgm.

The therapeutic value of amniotin in the menopause. Geist, S. H. and F. Spielman, Am. J. Obst. & Gynec. **23**: 697. 1932.

In a study of 43 cases treated over a period of seven months with amniotin in suppositories supplemented by amniotin by subcutaneous or deep injections, in 10 cases there was no improvement, in 22 cases there was varying improvements and in 11 cases there was considerable improvement. In the latter group of 11 cases the improvement was related to the appearance of vaginal bleeding after treatment. In the 10 cases showing no improvement there were five instances of radiotherapeutic castration. In the group of 11 cases showing considerable improvement 10 were associated with bleeding following treatment. In the group of 11 cases was one associated with kraurosis vulvae. In this case the improvement was steady and striking. It is difficult to determine the rôle played in alleviation of symptoms by the use of amniotin. The bleeding and relief of symptoms might have occurred without treatment. On the other hand, the question arises whether the amniotin initiated the necessary changes that produced bleeding and so caused an improvement. We may say that in one group of cases amniotin seems to have influenced the return of the menstrual period with a distinct alleviation of symptoms while the amniotin was exhibited, but the relief was not of a permanent nature. However, it is evident that the substitution of a single hormone, that is no longer being produced by the individual is not sufficient to prevent entirely the symptoms of menopause and it is certain that other factors are included in the problem of menopause.—S. H. Geist.

The therapeutic value of theelin in the menopause. Geist, S. H. and F. Spielman, Am. J. Obst. & Gynec. **23:** 701. 1932.

Twenty-five menopause cases in a series of 31 cases treated were studied in order to determine the effect of theelin, a biologically potent female sex hormone preparation. Seven of the 25 cases were definitely improved, three with the reëstablishment of menstruation. The others were either unimproved or so slightly improved as to be negligible. To patients with kraurosis on whom vulvectomy had previously been performed showed marked improvement of the itching. In several cases of natural menopause bleeding, possibly menstrual, followed the injection of theelin. The natural menopause seems to be more amenable to treatment than the artificial climacteric. In 14 cases of natural menopause, four were markedly improved and four were slightly improved. In 11 cases of artificial menopause four showed slight improvement.
—S. H. Geist.

The hormonal sterilization of the female organism. Haberlandt, L., Monatschr. f. Geburtsch. u. Gynäk. **87:** 320. 1931. Abst., Am. J. Obst. & Gynec. **22:** 512.

Haberlandt was the first to suggest the possibility of producing temporary sterilization by means of the injection of hormones. It was found that the substance which inhibits the ovary may be found not only in the ovary but also in the placenta. A few years ago the author outlined the clinical and eugenic indications for temporary sterilization. Since then, hormonal sterilization has been performed in women in Russia by means of injections of placenta extract. The difficulty consists in making a potent yet harmless preparation for clinical purposes. The substances used by Haberlandt in animal experiments are too weak for clinical use, but he hopes that the inhibitory element of the female sex hormone will soon be separated from the stimulating element and will be available for the purpose of temporary sterilization.

Blood exchange and hormonic reactions in parabiotic rats. Hill, R. T., J. Eper. Zoöl. **63:** (No. 1). 1932.

One hundred fifteen pairs of parabiotic twins of rats have been made, 70 of which have been used in various experiments. A colorimetric technique for measuring the rate of blood transfer has been developed. A given amount of dye is injected into the tail vein of one animal. A series of over one hundred colorimetric tests shows that at the end of one hour an average of about 25% of the dye is found in the uninjected animal. Nearly even distribution is established at the end of the sixth hour. It is obvious, from operative methods and the results of colorimetric tests, that all blood exchange takes place through capillaries. The effects produced by transmitted sex hormones have been studied under varied experimental conditions. It was found that two normal females in parabiosis have little, if any, effect on the oestrous cycles of each other. When normal females are in parabiosis with castrate females, the normal mates have fewer but longer oestrous cycles at the outset, but go into continuous oestrus after some months (two to four). The castrates of such pairs rarely show signs of oestrus. When one of a pair of normal females becomes pregnant, oeostrus is almost completely inhibited in both members. A normal male in parabiosis with a normal female has only slight effect on the sexual activity of the female.—Author's Abst.

Influence of the sex hormone upon the Kurloff bodies (Zur Beeinflussung der Kurloffkörper durch Sexualhormone). Hinteregger, F., Endokrinologie, **10:** 7. 1932.

The paper deals with the effects of castration and injection of sex-hormone preparations upon the number of Kurloff-bodies in the blood of guinea-pigs. The Kurloff-bodies do not disappear completely from the blood of castrated male guinea-pigs as pointed out by previous workers; nevertheless, the percentage of Kurloff-cells, i.e., of the monocytes and lymphocytes containing Kurloff-bodies, gradually declines until it reaches its minimum at about 6-8 weeks following castration. The effects of several sex-hormone preparations available on the European market upon the percentage of Kurloff-cells were studied and found to be variable and uncertain. Since other substances, such as adrenaline, may, upon injection, cause a rise in the number of Kurloff-bodies considerably more intensive than that effected by sex-hormones, the action of

the latter in regard to the Kurloff-bodies appears to be non-specific and, judging from the greater potency of lipoid extracts, related in some manner to fat-metabolism.—M. Zalesky.

The luteinizing substance of pregnancy urine. Katzman, P. A., L. Levin and E. A. Doisy, Proc. Soc. Exper. Biol. & Med. **28**: 873. 1931.

The daily administration of partly purified extract from urine of pregnancy to adult female rats produces a continuous state of estrin for the first 5 to 10 days, due to stimulation of the follicular apparatus. There is then a disappearance of the cornified cells from the smear for a period of 5 to 12 days after cessation of the injection. The ovaries become loaded with corpora lutea. The administration of three extracts to rats between the 14th and 19th days of pregnancy prolongs the gestation period, and usually results in dead and partially resorbed fetuses. The ovaries are more luteinized than normally and the authors believe that this factor is responsible for the retention of the fetuses.—M. O. L.

Female sex-glands and fat metabolism (Weibliche Keimdrüsen und Fettstoffwechsel). Kaufmann, C., Arch. Gynäk. **144**: 285. 1931.

The levels of total fat, fatty acid, and total cholesterol in the blood after 12-hour fasts are essentially constant. Normal women were given injections of Graafian follicle extract with high content of estrogenic hormone. In the next 2 hours the fatty acid and fat content of blood was raised 15 to 20%. Cholesterol was unaffected. Non-specific protein and serum did not cause such reactions. Extracts of pregnancy urine containing estrogenic hormone did not cause this reaction. Feeding of olive oil to costrated bitches caused a lipemia with return to normal blood fat in 5 hours. Estrogenic hormone from follicles or from pregnancy urine did not affect this. A special fraction of follicle fluid was prepared, said to be practically free from estrogenic hormone, and was found to greatly reduce the lipemia after olive oil feeding. Similar extracts of other organs and of blood serum did not give this effect. The author believes these results indicate a separate hormone in the follicle, related to fat metabolism.
—E. L. Sevringhaus.

An extract of the ovary, affecting metabolism (Untersuchungen über einen stoffwechselwirksamen Extrakt des Ovariums). Kaufmann, C., C. Müller and O. Mühlbock, Klin. Wchnschr. **11**: 14. 1932.

The authors prepared deproteinized extract from follicles with alcohol at a certain pH. This extract is not destroyed by boiling, like Kochmann's oobolin. After ingestion of this extract the metamorphosis of Rana temporaria is more rapid, while the control animals and animals to which the authors gave the extract from the urine of gravid mares, showed no metamorphosis. The effect of thyroxine is quite different, causing a disproportioned metamorphosis. Extract from the whole ovary, Kochmann's oobolin and folliculin are ineffective.
—E. Kodicek.

External evidence of hormone action following injection of urine of pregnant women into rabbits and guinea pigs. King, E. L. and A. G. King, Proc. Soc. Exper. Biol. & Med. **29**: 469. 1932.

Attention is called to the unreliability of the vaginal smears of rabbits, and to the opening of the vaginal membrane of immature guinea pigs when injected with the urine of a pregnant woman as criteria indicating the presence of the pregnancy hormones.—M. O. L.

A colorimetric determination of the estrus hormone (Eine kolorimetrische Bestimmung des Brunsthormons [Menformon]). Kober, S., Biochem. Ztschr. **239**: 209. 1931.

Five micrograms (about 55 mouse units) of the purified hormone (Menformone) is measured into a small test tube, and the solvent evaporated. Of a mixture of equal parts concentrated sulphuric acid and phenol-sulphonic acid (o and p) 0.2 cc. is then added, the mixture heated in a boiling water bath for two minutes, cooled and 0.2 cc. water added. It is then quickly heated to boiling, 0.8 cc. of water added, and immediately cooled. As a color standard a solution of cresol red (acid) may be used, 10 mgm. in 100 cc. The Autentrieth

colorimeter may be used, but the wedge containing the standard solution should be calibrated by the use of color mixtures obtained from actual solutions of hormone of various concentrations, since the color is not directly proportional. Five micrograms of hormone give approximately the same color as 25 micrograms of cresol red.—B. S. Walker.

Further studies of the follicular-corpus luteum relationship in the rabbit. Leonard, S. L., F. L. Hisaw and H. L. Fevold, Am. J. Physiol. **100**: 111. 1932.

Corporin (acid-alcohol extract of corpus luteum) and follicular hormone (oil soluble theelin) were injected into sexually mature female rabbits, the oestrin holding the effects of corporin in abeyance for at least nine days, after which the latter initiated progestational endometrial modification when the dosage of theelin was lowered. A much larger dosage of oestrin was required to obliterate the endometrial modifications of early pregnancy than was necessary to obliterate changes of similar degree caused by the injection of corporin into a rabbit castrated in heat, but the non-castrate animals required only slightly more corporin than the castrate for the production of progestational changes. Such changes could not be maintained indefinitely by these hormones either singly or in combination and the amount of corpin which in five days could produce a definite modification did not inhibit ovulation in a properly stimulated non-castrate rabbit in heat. These results indicate a quantitative relationship of the two ovarian hormones and an apparent antagonism on the basis of a physiological competition for control of the endometrium which the authors consider to be conditioned by theelin and depleted by secretion in response to corporin, both of which processes cannot occur simultaneously in the same cell.—Minna Emch.

The effects of x-rays on the gonads of Amphibian larvae. Levine, W. T., J. Exper. Zoöl. **62**: (No. 2). 1932.

Experiments were made to determine the relative resistance to x-rays of the two types of antagonistic sex inductors in gonad of anurans. One inductor is localized in the cortex of the sex gland, and produces a female-differentiating substance, while rete cells of the medulla induce male differentiation. Irradiation of larval testes shows them to be highly resistant, and only after relatively high dosage is there shrinkage after about ten weeks. Loss in size is due to resorption of spermatogonia. With doses from 4000 to 10,000 r. units and protection with lead screen except for the gonad region, larvae survive eight to 14 weeks after treatment. After the second week degeneration of oocytes and auxocytes occurs, accompanied by a relative increase in granulosa cells. After eight weeks the ovaries shrink to the size of testes and lose all germ cells save peripherally placed primary oogonia. Granulosa, stroma, and some rete cells then fill the greater part of the gonad. With sublethal doses (1500 to 4000 r. units) the same initial stages of involution are observed, but after females have remained in a sexually neutral state for several weeks, they exhibit ovarial regeneration by mitosis of surviving primary germ cells. The high resistance to irradiation of granulosa cells, presumably the female sex inductors, together with the low sensitivity of primary germ cells, prevents total sterility or sex reversal.—Author's Abst.

Does folliculin affect the plumage of pigeons (La folliculine agit-elle sur le plumage du Pigeon)? Lipschütz, A., Compt. rend. Soc. de biol. **108**: 690. 1931.

A dose, 30 times greater than one influencing the plumage of poultry, had no effect on the plumage of pigeons.—J. C. D.

Rat and mouse units of folliculin (Unité-rat et unité-souris de folliculine). Lipschütz, A., Compt. rend. Soc. de biol. **108**: 754. 1931.

Fifty-eight mice and 136 rats were given divided doses of folliculin extracted from the urine of pregnancy. Rats required three times as much folliculin to produce a given effect as did mice, i.e., a rat unit is three mouse units.—J. C. D.

Aphrodisiacs and estrus hormone (Aphrodisiaka und Brunsthormon). Ludwig, F. and J. von Ries, Schweiz med. Wchnschr. **62**: 401. 1932.

Yohimbin in doses of 0.1 mgm. and 0.005 mgm. of cantharidin gave a positive Allen-Doisy test. The uterus was not enlarged. The Allen-Doisy test was not specific, without control of the uterus. The authors distinguished the hormone from the aphrodisiacs by infra-red light. After application the hormone was 5 times more efficacious, but the aphrodisiacs lost their effect.
—E. Kodicek.

The testicular hormone. Extraction and tests upon castrated and infantile mice (Das testikuläre Hormone; Extraktion und morphologische Wirkungen auf infantile und kastrierte männliche Mause). Martins, T., Endokrinologie, **7**: 180. 1930.

Lipoid extracts of bull testicle prevent seminal vesicle atrophy, and produce premature puberty when injected into mice.—B. C.

The incidence, diagnosis and treatment of functional sterility. Mazer, C. and I. Andrussier, Am. J. Obst. & Gynec. **22**: 46. 1931.

The dependence of ovarian function upon hormonal stimulation from the anterior pituitary gland and the compensatory hyperfunction of the latter in cases of primary ovarian failure are herein emphasized. The normal menstrual cycle depends upon the balanced activity of the two ovarian hormones; the female sex hormone generated by the graafian follicle produces growth and vascularization of the uterus, the lutein hormone generated by the corpus luteum produces premenstrual endometrial changes preparatory to the reception of a fertilized ovum. Evidence is given that 16 of the group of 37 regularly menstruating sterile women were probably subject to anovular menstruation as shown by the simultaneous absence of a premenstrual endometrium and a demonstrable quantity of female sex hormone a day or two before the onset of the expected flow. The Frank and Goldberger test for the blood level of female sex hormone is of great value in the diagnosis of functional sterility in regularly menstruating women, but is of little value in the diagnosis of this condition associated with menstrual derangements. The recovery of a demonstrable quantity of anterior pituitary sex hormone from the blood of women suffering from functional sterility is pathognomonic of primary ovarian failure. Normal fertile women and those suffering from pituitary hypofunction rarely, if ever, show a demonstrable quantity of the hormone except during pregnancy. Low dosage irradiation of the affected endocrine glands was successful in re-establishing menstrual periodicity in more than 50% of 38 women thus treated; organotherapy is far less effective. The number of succeeding pregnancies is relatively equal in the two groups treated, respectively, by x-ray stimulation and organotherapy.—Authors' Summary.

Dual endocrine activity of the testes. McCullagh, D. R., Science, **76**: 19. 1932.

By the use of fat solvents there can be obtained from the testes or the urine and blood of normal subjects a substance, "androtin," that prevents the atrophy of the prostate and seminal vesicles following castration (rats). This is the substance that causes comb growth in capons. It does not prevent the hypertrophy of the pituitary and the adrenals that commonly follow castration. Destruction of the germinal epithelium of the testes causes pituitary hyperfunction but not atrophy of the secondary sex glands. An aqueous testicular extract has been obtained that prevents pituitary hypertrophy after castration. This new testicular hormone is named "inhibin." It is postulated that clinical prostatic hypertrophy is due to a failure in the production of inhibin which conditions pituitary hyperfunction and this in turn results in overstimulation of the secondary sex glands.—R. G. H.

The effect of prolan on the sex function of young male animals (Die Beeinflussung der Geschlechtsfunktion junger männlicher Tiere durch Prolan). Neumann, H. O. and F. Peter, Zentralbl. f. Gynäk. **56**: 34. 1932.

The authors used prolan prepared by I. G. Farbenindustrie on 10 litters, a total of 26 immature male mice. Eight experimental animals were treated from the 20th to the 76th day of life, with total dosages ranging up to 2000 R.U. of Prolan A and B. The control animals gained 13-19 gms. and weighed

18-23 gms. at 67 days, while the treated mice gained only 6-8 gms. and weighed from 11 to 13 gms. at the 67th day. The treated animals did not mate during the experiment, although the controls sired litters. The testes of the treated animals weighed from 32 to 39 mgm., and those of the controls, 79 to 114 mgm. The accessory organs were not increased. Active sperm formation was found in the tubules of the control mice, but in the treated series all stages of maturity inhibition occurred in the tubules. Most tubules showed only spermatid formation. The interstitial cells of the treated mice showed an enormous increase.—E. T. Engle.

Activity of commercial folliculin (Valoración biológica de los preparados comerciales de foliculina). Novelli, A., Rev. Soc. argent. de biol. **7**: 494. 1931.

Eleven samples were tested according to the Marrian and Parkes method. The rat unit used was the minimum amount necessary to produce estrus in 50% of castrate rats, using 20 animals in each test. The declared potency was found in only 1 case.—J. T. Lewis.

Effect of specific (testifortin) and non-specific (Kovoprotin) substances upon prostate and seminal vesicle involution in the castrated rat (Zur Beeinflussung der Sexualkonstitution kastrierter Rattenmännchen durch spezifische und unspezifische Reize). Prange, F., Endokrinologie, **7**: 256. 1930.

Bilaterally castrated rats respond to subcutaneous injections of a male hormone preparation by a cessation of involution of prostate and seminal vesicles, but do not respond to novoprolin, an albuminous substance. Under treatment there is some evidence of regeneration of accessory gland tissue.—B. C.

Oestrus-substance under pathologic circumstances (Ueber das Auftreten eines Brunststoffes unter pathologischen Verhaltnissen das Auftreten und Verschwinden einer östrogenen Substanz in Bakterienkulturen). Silberstein, F., K. Molnar and E. Engel, Wien. klin. Wchnschr. **45**: 559. 1932.

The authors found a substance, which gave a positive Allen-Doisy test in the blood of animals with carcinoma and sarcoma treated with radium. Also they extracted this substance by alcohol-acetone-ether from cultures of staphylococcus albus, and of colibacteria on 2% agar and in bouillon. They injected 0.1 cc. 3 times to castrated mice and found a positive Allen-Doisy test with young cultures of staphylococcus (12-24 hours) in bouillon and agar. Old cultures were inefficacious. The young cultures of bacterial coli on agar also gave a positive Allen-Doisy test, but not the extracts from bouillon.—E. Kodicek.

On the follicular hormone (Zur Kenntnis des Follikelhormons). Skarzynski, B., Ztschr. f. physiol. Chem. **196**: 19. 1931.

The ultra violet absorption curves of the crystalline follicular hormone, prepared by the methods of Butenandt and of Marrian, were determined and compared. The curves are very similar. From this evidence the author believes the active material to be identical but adsorbed on different inert materials dependent on the method of purification.—J. M. Curtis.

The excretion of oestrin by women. Smith, G. V. and O. W. Smith, Am. J. Physiol. **100**: 553. 1932.

On the basis of the authors' previous finding that progestin causes the excretion of injected oestrin in rabbits (Am. J. Physiol. **98**: 578. 1931) a test for corpus luteum and hence presumably follicular activity in women was evolved. Oestrin (200-400 R.U. daily) was given orally to women, whose urines were followed for its excretion, over a period of one or two months. Eight cases are reported, including four amenorrheic patients, three sterile, and one normal control. The results would indicate that in women as in rabbits oestrin is excreted only when the organism has been exposed to the action of corpus luteum. It appears possible by this means to differentiate between a persistent corpus luteum, irregular appearance or total absence of corpus luteum, and normal cyclic activity of the corpus luteum.—Authors' Abst.

The effect of the injection of urine from pregnant mammals on ovulation in the rabbit. Snyder, F. F. and G. B. Wislocki, Johns Hopkins Hospital Bull. **48**: 362. 1931.

The urines of pregnancy of various animals (macaque monkeys, rabbits, rats, cats and dogs) do not produce ovulation in mature, healthy, isolated rabbits. The ovulation test in the rabbit does not completely parallel the similar mouse test as reported in the literature. The urines of pregnancy from monkeys and anthropoid apes have been described as giving positive tests in the mouse. In our experiments the urine from pregnant macaque monkeys has given negative tests in the rabbit. Of the two tests available for the diagnosis of pregnancy, the ovulation test in the rabbit appears to be more specific than the mouse test. The observation that human urine of pregnancy produces ovulation in mature rabbits has been confirmed.—Authors' Summary.

Prenatal growth of human testes and ovaries. Wald, H. and R. E. Scammon, Proc. Soc. Exper. Biol. & Med. **29**: 416. 1932.

The growth in weight of the testes, as determined in a series of 89 human fetuses, 16.3 to 3600 gms. total weight, was quite comparable to that of the body as a whole and that of most of its major parts and organs. Although the growth of the absolute weight of the testes is thus proportional to growth in body weight in the fetal period, the relative weight of the testes with respect to body weight undergoes a reduction from 0.143% at 3 months to 0.023% at birth.—M. O. L.

A positive Friedman test in a case of teratoma testis with gynecomastia. Weinstein, G. L. and F. S. Schofield, Proc. Soc. Exper. Biol. & Med. **29**: 852. 1932.

A teratoma of the testis (confirmed by microscopic examination) was removed from a 24-year-old patient who showed moderate gynecomastia. Three months later, with no clinical evidence of metastasis of the tumor, the patient's urine gave the same positive Friedman test as pregnancy urine.—M. O. L.

The hormonal regulation of the uterine epithelium (Untersuchungen über den Schleimhautzyklus in der Tuba uterina, seine hormonale Regulierung und die Bedeutung des Tubensekrets für die Vitalität der befruchteten Eier). Westman, A., E. Jorpes and G. Wildström, Acta obst. et gynec. Scandinav. **11**: 279. 1931.

The authors confirm the observations of Corner and Allen that fertilized tubal ova of the rabbit degenerate shortly after castration. Cauterization of the corpora lutea alone gives the same effect as castration. The reason is stated to be that in the absence of the active principle of the corpora there is not the normal transformation of ciliated epithelium to secretory cells. Extracts of cow corpora and whole ovaries of sow containing an active principle cause the transformation of tubal epithelium which is necessary for the viability of tubal ova. Seventeen rabbits were used.—E. T. E.

Variability of pigmentation in the hypophysis and parathyroids of the gray rat (Mus norvegicus). Addison, W. H. F. and Doris Fraser, J. Comp. Neurol. **55**: (No. 2). 1932.

Melanotic pigment is present in the hypophysis of the adult Norway rat, both wild and captive, in the majority of cases. When present, it is usually confined to one part of the organ. It is seen most frequently in the pars intermedia, but is also found in the pars distalis and on the margins of the pars nervosa. The pigment is in melanophores lying in the connective-tissue septa. There is no apparent difference in the incidence of pigmentation in males and females, nor is there any observed relation of gestation to pigmentation. Pigmentation within the pars intermedia was seen as early as at two months of age, but is not of constant occurrence even in old rats. Pigment within the parathyroids has been found in a small number of cases, in both wild and captive gray rats. The pigment cells lie in the connective-tissue septa between the epithelial cell masses, but has not been seen in the adjoining thyroid. When present, it may occur in only one of the parathyroids, or in both. The parathyroids may be pigmented in the presence or absence of pigment in the hypophysis.—Authors' Abst.

The dominant rôle of the pars anterior of the hypophysis in initiating amphibian metamorphosis. Allen, B. M., Anat. Rec. **54**: (No. 1). 1932.

The pars anterior of the hypophysis was removed from tadpoles, metamorphosing toads, and adults of Bufo halophilus at various stages, and transplanted under the skin of the top of the head of recipient tadpoles at a stage of 1 mm. (in some series 2 to 3 mm.) hind-leg length. When taken from donors in process of metamorphosis, or in which that process had been completed, the transplant induced metamorphosis in the recipient. If, however, the donor had hind legs of less than 6 mm. total length, no acceleration of metamorphosis was induced. This limit of development mentioned is one which may be reached by hypophysized and thyroidectomized tadpoles. The difference in influence of the transplant is qualitative and not quantitative, as shown by preliminary histological studies. Although the basophile cells are present in the pars anterior of the hypophysis of these early stages, they are few in number and stain faintly in contrast with the greater development of the eosinophile cells. Transplants that accelerate metamorphosis do so as a result of the marked enlargement and colloid formation that they induce in the thyroid glands. This effect is produced by the pars anterior of the hypophysis only after it has reached a certain stage of development marked histologically by an increase in the proportion of the basophile cells.—Author's Abst.

The fat metabolism hormone of the anterior lobe of the pituitary. Demonstration, preparation and properties of the hormone (Das Fettstoffwechselhormon des Hypophysenvorderlappens. I. Nachweis, Darstellung und Eigenschaften des Hormons). Anselmino, K. J. and F. Hoffmann, Klin. Wchnschr. **10**: 2380. 1931.

The watery extract of the dry powder of pituitary anterior lobes produces in rats a marked increase of the acetone bodies of the blood which is mainly due to an increase of Beta-oxybutyric acid while acetone and acetic acid are only slightly changed. The effect lasts several hours; its intensity and duration vary according to the amount of extract injected. The authors assume the active substance to be identical with a metabolism hormone of the anterior lobe. It is insoluble in ether, chloroform, and concentrated alcohol. Although corresponding in some chemical and physical respects it is not identical with the Aschheim-Zondek sexual hormone from which it can be separated through adsorption of the latter by charcoal. It is also not identical with the growth hormone. It is excreted to a certain extent with the urine. A unit of the acetone body-increasing principle is defined as the smallest amount of it which increases the acetone bodies in the blood of adult male rats of 150 grams of weight two hours after injection to the level of 10 milligram per cent.

—W. Raab.

Hormone of posterior lobe of hypophysis in blood of gravidas (Vermehrung des Hypophyseninterlappenhormons im Blute und Art und Schwere der klinischen Erscheinungen bei der Nephropathie und Eklampsie der Schwangeren). Anselmino, K. J. and F. Hoffmann, Arch. f. Gynäk. **147**: 621. 1931. Abst., J. A. M. A. **98**: 1043.

The authors determined the antidiuretic component of the hormone of the posterior lobe of the hypophysis and the blood pressure increasing substance in the blood of twenty-one gravidas with nephropathy and eclampsia. The demonstration of the antidiuretic substance was possible in nearly all cases with edema. In severe cases the quantity of the antidiuretic substance was larger than in mild cases. From 20 to 30 hours after delivery the antidiuretic substance had generally disappeared from the blood, except in one case of puerperal eclampsia. In the blood of healthy gravidas and of gravidas with dropsy, the antidiuretic substance could not be demonstrated. The authors show that there is a relation between the content of the blood in the antidiuretic substance and the severity of the clinical symptoms, for usually when an improvement was observed there was also a decrease in the antidiuretic substance. The blood pressure increasing substance was demonstrable in all cases in which the blood pressure exceeded 180 mm. of mercury. It was also observed that the antidiuretic component of the hormone of the posterior pituitary and the blood pressure increasing substance may occur in the blood independent of each other.

Concerning the anterior pituitary hormone in the cerebrospinal fluids (Ueber Hormone des Hypophysenvorderlappens im Liquor cerebrospinalis). Aronowitsch, G. D., Endokrinologie, **7**: 113. 1930.

Using the infantile mouse ovary as a test, the hormone can be demonstrated in spinal fluids of pregnancy, but not in others. Only a third of the cases reacted positively. Tests made on urine, blood serum, and amniotic fluids gave positive and even more evident results. The author concludes that the hormone reaches the spinal cavity through the blood stream rather than directly.—B. C.

The effect of the injection of hypophyseal extract in advanced lactation. Asdell, S. A., Am. J. Physiol. **100**: 137. 1932.

Repeated daily injections of alkaline extract from sheep hypophyses prevented for a time the normal decline of milk yield in 3 goats with advancing lactation.—R. G. H.

Behavior of the lipoid granulations in the hypophysis of dogs with unilateral ovariectomy (Comportamento delle granulazioni lipidiche nelle ipofisi di cagne sottoposte a ovariectomia unilaterale). Comel, M. C. B., Boll. d. Soc. ital. di biol. sper. **6**: 789. 1931.

Right unilateral ovariectomy in dogs (number not stated) before and at the age of puberty caused the following modifications in the lipoid granules of the hypophysis. Six months after the operation the hypophysis is formed almost entirely by large cells, which are found in small numbers in the normal hypophysis. Droplets and lipoids were found in small numbers in the normal hypophysis. The cytoplasm of these cells shows a reddish color. The vesicles lack granules and lipoid droplets. In the hypophysis of dogs killed 2, 3 or 4 months after right unilateral ovariectomy there is seen the gradual disappearance of droplets and intracellular and extracellular granulations. The disappearance of granulations is seen more clearly the longer the interval after operation. The hypophyses were fixed in formalin at 10% and stained successively with Sudan III and hemotoxylin.—C. M. Cerrato.

The development of the hypophysis of the cat (Felis domestica). Brahms, S., Am. J. Anat. **50**: (No. 2). 1932.

Embryos and kittns ranging from the eleven-to-twelve somite stage to 275 mm. in length were examined. This study furnished evidence that the hypophysis is a structure determined by the cephalization of the vertebrate embryo. Comparison of the works of various workers on several animals indicates that the hypophysis is fundamentally the same in all vertebrates. It is of purely ectodermal origin. Rathke's pouch is not an active evagination, but an expression of the ventral rotation of head material attendant upon cephalization. Continued rotation results in closure of the pouch to form the hypophyseal sac and stalk. In the cat, the ventral wall of the sac gives rise to the main body of the pars distalis by proliferation. The infundibular diverticulum, an outgrowth from the floor of the diencephalon, comes to be surrounded by fused pars intermedia and pars distalis. The hypophyseal stalk persists throughout development and at least traces are seen in 275-mm. kittens. The pars tuberalis originates on the ventrocaudal wall of the sac, as a pair of lateral lobes, on a ridge from which the hypophyseal stalk takes its origin. These lateral lobes grow toward the floor of the brain and each gives off a ventral and a dorsal horn which ultimately fuse, respectively, after the dorsal horns have grown around the neck of the infundibular diverticulum. The early relation between the pars distalis and the hypophyseal stalk and the lateral lobes is retained. The pars tuberalis is at no time related to the pars intermedia.—Author's Abst.

Laurence-Moon-Biedl's syndrome (complicated dystrophic imbecility) (Imbecillitas dystrophica complicata) observed in brother and sister. Bing, R., Norsk. mag. f. laegevidensk. **92**: 956. 1931. Abst., J. A. M. A. **98**: 440.

Bing states that only 36 cases of this syndrome have been reported in the literature to date. The main symptoms are imbecility, adiposogenital dystrophy, atrophy of the optic nerve or retinitis pigmentosa, and polydactylism. He presents two additional cases, in a boy aged 17 and a sister aged 14. The parents and the four other children are normal. Treatment with calcium, thy-

roid and pituitary extract, while without effect on the vision, resulted in loss of weight, rise in basal metabolism, and a change from dullness and apathy to greater animation and interest in the surroundings.

The posterior pituitary hormone in metabolism; the effect of pitressin upon the carbohydrate reserves of the normal rabbit. Bischoff, F. and M. Louisa Long, Am. J. Physiol. **97**: 215. 1931.

Doses of pitressin which are effective in producing hyperglycemia and lactic acidemia in the rabbit are pharmaceutical and not physiological. They approach the lethal dose. Hyperglycemia and lactic acidemia do not run parallel. The toxic effect of pitressin is not reduced when given as a continuous intravenous injection and when so given may be more pronounced than the effect of a single intravenous dose. Pharmaceutical doses of pitressin, whether given intravenously or subcutaneously, produce no changes in the glycogen reserves of the muscle outside the limits of normal expected variation. A possible but not clearly established increase in liver glycogen takes place. No changes without the normal limit in the blood amino-acid nitrogen, urea nitrogen, or cholesterol are produced. As measured by the oxygen capacity, a pharmaceutical dose of pitressin increases the blood volume by 10% in the course of three hours. The muscle sugar rises above the resting level during a pitressin hyperglycemia.—Authors' Summary.

Transplantation and extirpation of the pituitary rudiment and the effects upon pigmentation in the urodele embryo. Blout, R. F., J. Exper. Zoöl. **63**: (No. 1). 1932.

The hypophyseal rudiment was transplanted from urodele embryos into others of the same age before it was visibly developed. The transplants functioning in addition to the gland normal to the animal produced an excess secretion, the effects of which have been studied. The grafts have been of two types —those in which the entire pituitary region, including nervous tissue, was taken and those in which only the epithelial portion was used. Transplants of the entire pituitary region develop in an essentially normal manner. In addition to pituitary tissue, there develops from the grafted tissue a mouth cavity with associated structures and a small brain vesicle. The pituitary of the transplant differentiates concomitantly with the normal gland of the host. The cord-like arrangement of cells appears simultaneously in both. When the epithelial portion is transplanted alone, the pituitary does not develop. The epithelial portion of the pituitary is developmentally dependent upon its association with the neural portion. The transplant brings about many changes, among them the increase in pigmentation with which this paper deals. Other effects will be presented later. The pigment increase is due to two distinct reactions, melanophore expansion and the accumulation of non-chromatophoric pigment. This reaction shows definitely the function of the transplanted pars intermedia. Function begins before feeding at a stage when the limb bud first bifurcates.—Author's Abst.

The rôle of the anterior lobe of the pituitary gland in growth, with special reference to the teeth and maxillae. Downs, W. G., Arch. Path. **12**: 37. 1931. Abst., J. Nerv. & Ment. Dis. **76**: 73.

For this study mice were injected with extracts containing the growth hormone and effects on the teeth and maxillae followed grossly and microscopically. Chemical studies were made on the whole tissues of these animals. Dogs were the subject of hypophysectomies and injections of the growth hormone, and the results followed grossly and microscopically. These studies indicated that the growth hormone of the pituitary affected the size of jaws and consequently spacing of the teeth, but had no specific effect on the teeth themselves. Some interesting observations were made of the effects of this hormone on tissue chemistry, in particular fat deposition.

The use of the fistula method in a study of the function of the hypophysis (Die Anwendung der Fistelmethode beim Erforschen der Funktionen der Hypophysis). Dubowik, I. A., Endokrinologie, **7**: 100. 1930.

A description is given of the construction and use of a glass fistula tube which may be used in studying the hypophysis of a frog.—B. C.

Effect of antero-pituitary hormones upon blood sugar. Eidelsberg, J., Proc. Soc. Exper. Biol. & Med. **29**: 959. 1932.

The administration of 100 units of gonad-stimulating hormone from pregnancy urine to rabbits was usually followed by increase of 100 to 175 mgms. per cent in the blood sugar content. Administration of a preparation of pituitary growth hormone caused a slight rise or drop in the blood sugar level. —M. O. L.

Disturbance of carbohydrate metabolism in normal dogs injected with the hypophyseal growth hormone. Evans, H. M., K. Meyer, Miriam E. Simpson and F. L. Reichert, Proc. Soc. Exper. Biol. & Med. **29**: 857. 1932.

Of four dogs given daily intraperitoneal injections of anterior pituitary growth hormone (free of gonad-stimulating hormone) for 8-9 months, two, one male and one female, showed glycosuria. The fasting blood sugar in each dog was about 230 mgm. per cent. The other two dogs, litter mates under identical treatment, showed such disturbance of carbohydrate metabolism. The results indicate that insulin and the growth hormone are antagonists, but that "constitutional" differences in individuals may mask the antagonism.—M. O. L.

The calcium and phosphorus in the blood plasma of hypophysectomized dogs (Calcium et phosphore du plasma sanguin des Chiens hypophysoprives). Gerschman, R., Compt. rend. Soc. de biol. **108**: 494. 1931.

In 8 dogs this operation was without influence on these constituents. —J. C. D.

Use of the rabbit in the Aschheim-Zondek test for pregnancy. Grant, W. H., N. Zibel and H. E. MacMahon, New England J. Med. **206**: 893. 1932.

A relatively simple hormone test for pregnancy, based on the early work of Aschheim and Zondek, is described and the results of the test in 100 cases are reported with an accuracy of 96%. The possibilities of error, which should be borne in mind in such biological tests, are considered. Both the clinical and the pathological aspects of the study are included in the report.—J. C. D.

Time of appearance and duration of pregnancy cell types in hypophysis of the rat. Haterius, H. O., Proc. Soc. Exper. Biol. & Med. **29**: 962. 1932.

Pregnancy cell types appear in the anterior lobe on the third and fourth days following fertile or infertile copulation. These cell types increase in number and in size until the twelfth day and, in the event of pregnancy, persist throughout the time of gestation. In all instances they disappear upon resumption of the oestrous cycle. The pituitary of the pseudopregnant animal is identical in its changes with that of pregnancy. The pregnancy cell type in this circumstance persists until the twelfth day, disappearing upon the return of oestrus. Pregnancy cell types occur coincidental with a dominant luteal ovarian phase, and it is believed, on the basis of this and previous experimental evidence, that the luteal factor is responsible for their genesis. Their significance, however, remains obscure.—Author's Abst.

Concerning the etiology of hyperplasia of the endometrium. Hofbauer, J., Surg., Gynec. & Obst. **52**: 222. 1931. Abst., Biol. Absts. **6**: 1931.

In an unstated proportion of 28 guinea pigs treated parenterally with extract of beef anterior pituitary, and more markedly in 18 guinea pigs into which bits of fresh anterior pituitary were transplanted there were produced (so long as the ovaries were preserved) conditions in the uterine mucosa and the ovaries practically identical with those in human endometrial hyperplasia; after oöphorectomy the process was limited to the basal portion of the endometrium. These observations suggest that hyperplasia may reasonably be regarded as the manifestation of an overactivity of the anterior pituitary lobe, the internal secretion of the ovary being essential for the changes occurring in the upper part of the uterine mucosa, while the basal layer is entirely under the control of the anterior pituitary lobe.

Overactivity of the posterior lobe of the pituitary as the cause of nephrosis and eclampsia of pregnancy (Uber die Entstehung der Nephropathie und Eklampsie der Schwangeren durch Uberfunktion des Hypophysenhinterlappens). Hoffman, F. and K. J. Anselmino, Klin. Wchnschr. **10:** 1442. 1932.

Eleven cases of nephrosis of pregnancy and 10 of eclampsia are considered. Examination of the ultrafiltrate from blood plasma (previous paper) showed the presence of anti-diuretic substance in all except one case in which there was no edema. A pressor substance was present in all cases where the blood pressure was over 180 mm. In control determinations on the ultrafiltrates from the blood of non-pregnant and normal pregnant individuals no demonstrable amounts of the anti-diuretic or pressor substances were found by using the authors' methods. The authors believe that there is a parallelism between the amounts of anti-diuretic and pressor substances in the blood and the severity of the symptoms of nephrosis and eclampsia and that the cause of nephrosis and eclampsia is due to increased activity of the posterior lobe of the pituitary. —E. L.

The fat metabolism hormone of the anterior lobe of the pituitary. Metabolic action and regulation of the hormone (Das Fettstoffwechselhormon des Hypophysenvorderlappens. II. Stoffwechselwirkungen und Regulationen des Hormons). Hoffmann, F. and K. J. Anselmino, Klin. Wchnschr. **10:** 2383. 1931.

The metabolism-active extract of the pituitary anterior lobe as described in the foregoing article increases the acetone bodies in the blood of man. The summit of the curve is attained within two to three hours. The blood sugar remains unchanged. The extract of 600 to 1000 milligrams dried gland decreases the basal metabolism in man from 5 to 15%; it increases the specific dynamic action somewhat. After the intake of a meal rich in fat the active principle appears in the human blood, as could be demonstrated by the blood acetone raising effect in rats of the injection of human serum taken before and at intervals after the fat intake. The active principle in the serum was found to be identical with the one contained in the anterior lobe extracts. After the intake of larger amounts of carbohydrates or proteins the active principle did not appear in the human blood. On the other hand, it was found in the blood of a starving dog and was again removed from there through the administration of glucose and insulin. The authors assume that the "fat metabolism hormone" of the pituitary anterior lobe is secreted in all conditions where fat is oxydized in the body.—W. Raab.

Pituitary and thyroid. VII. Anterior lobe extract and sensitiveness to anoxemia (Hipófisis y tiroides. VII. Extracto de lóbulo anterior de hipófisis y sensibilidad a la anoxemia). Houssay, B. A. and C. T. Rietti, Rev. Soc. argent. de biol. **8:** 53. 1932.

Rats were injected with alkaline anterior lobe extract (Evans and Simpson) intraperitoneally daily for 3 days. On the 3rd day they were submitted to progressively decreasing barometric pressure. They died before the normal controls. Completely thyroidectomized rats died after the controls. Partially thyroidectomized rats died before the controls. Completely thyroidectomized rats treated with anterior lobe extract died in the same conditions as those thyroidectomized who had not been injected. Therefore anterior lobe extracts product hypersensitiveness to anoxemia due to hyperthyroidism.—J. T. Lewis.

Haemoglobin content and number of red blood cells in hypophysectomized dogs (Hémoglobine et nombre d'érythrocytes des Chiens hypophysoprives). Houssay, B. A., M. Royer and O. Orias, Compt. rend. Soc. de biol. **108:** 496. 1931.

Both haemoglobin and number of red cells were reduced in the hypophysectomized animals.—J. C. D.

Concerning the conditions affecting secretion of the anterior lobe of the pituitary and its effects on the course of the cycle (Über die Bedingungen der Hypophysenvorderlappensekretion und ihre Folgen für den Ablauf des Zyklus). Kuschinsky, G., Arch. f. exper. Path. u. Pharmakol. **162:** 183. 1931.

The author sought to determine the action of "Prolan" and "Prähormon" on the gonad-stimulating potency of the anterior lobe. Mature female rats,

120-190 gms. body weight, were treated with 25 R.U. per day for short periods, usually 10 days, after which the anterior pituitaries of the treated animals were transplanted into 24-25-day female rats, each rat receiving two glands on two successive days. These infantile rats were very small (22 gms.). The weights of the ovaries of the test rats which received pituitaries from prolan-treated animals were slightly less than the ovaries of animals which received implants from normal females. After prolan treatment of rats, castrated 8-10 days, the results are inconclusive. In two cases the actual ovarian weights from rats implanted with prolan-treated castrates were higher than untreated castrates, in four cases were less, and in one set there was no difference. Implants from normal rats treated 12-13 days with folliculin gave a lesser ovarian response than normal, and about the same degree as prolan-treated donors. The author gives a discussion of the relation of these findings to the question of the regulation of the human cycle—E. T. E.

The modification of the Aschheim-Zondek test by the use of blood serum; preliminary report. Laszlo, A. E., Am. J. Obst. & Gynec. **23**: 889. 1932.

A modification of the Aschheim-Zondek test for pregnancy is presented in which a single subcutaneous injection of 1 cc. of blood serum into an undeveloped female mouse of 6 to 8 grams is used. A reaction, in all respects similar to the Aschheim-Zondek, is obtained after an interval of 72 hours. With the above method there has been little mouse mortality. It seems reasonable to assume that in pregnancy there is an increased amount of female sex hormone in the blood serum and that its increase in the urine is due to this fact rather than to any selective action of the kidney.—Author's Summary.

Quantitative difference in a rabbit-ovulating dose of prolan and anterior pituitary extract. Leonard, S. L., Proc. Soc. Exper. Biol. & Med. **29**: 812. 1932.

The ovulating dose of an anterior pituitary extract for rabbits is very much less than that of prolan when the potency of these two substances is standardized on immature female rats. This difference in quantitative activity of prolan and an anterior lobe extract suggests a physiological difference between the two substances.—Author's Summary.

The question of the corpus luteum producing factor in the guinea pig hypophysis (Sur la question du facteur lutéinisant dans l'hypophyse du Cobaye). Lipschütz, A., Compt. rend. Soc. de biol. **108**: 646. 1931.

Grafts of guinea pig hypophysis hasten the maturity of rats. The ovaries may show growth but fail to show any corpora lutea later. Evidently in the guinea pig gland, the hormone producing maturation of the follicles is present but that stimulating the formation of corpora lutea is either absent or much weaker than in the rat hypophysis.—J. C. D.

On hormothyrin, the thyroid-activating hormone of the anterior lobe of the hypophysis (Ueber Hormothyrin, das schilddruesen-anregende Hormon des Hypophysenvorderlappens). Paal, H., Klin. Wchnschr. **10**: 2172. 1931.

The presence of the "thyroid-activator" in the prehypophysis, as demonstrated by the work of P. E. Smith (1922), E. Uhlenhuth and S. S. Schwartzbach (1926) and others is confirmed in experiments on the resistance of white mice against acetonitril (Reid Hunt test). Extracts made from whole anterior lobe increase the resistance of the white mouse against acetonitril. After thyroidectomy this protective effect is missing. Protection may be obtained by injecting into white mice the serum of normal rabbits injected with anterior lobe extracts, but not from the serum of rabbits which were injected with anterior lobe after thyroidectomy. Injections of prolan do not increase the resistance of the white mice against acetonitril. It is concluded that the protective effect of anterior lobe extract against acetonitril poisoning produced by anterior lobe injections is due to the activation of the thyroid caused by these injections and that the anterior lobe contains a thyroid-activating substance not contained in the prolan fraction of the prehypophysis. A new name—hormothyrin—is suggested for this substance called "thyroid-activator" by Uhlenhuth.—E. Uhlenhuth.

Relation of the hypophysis and ovaries to experimentally-induced uterine bleeding in monkeys. Saiki, S., Am. J. Physiol. **100**: 8. 1932.

Menstruation-like bleeding from the uterus was caused by the injection into immature monkeys of an extract of the hypophysis (11 positive cases in 12). Intervals between the last injection and the external bleeding were from 4 to 9 days, and the duration of the external bleeding was from 5 to 7 days. This menstruation-like bleeding was produced 2 or 3 times at short intervals. Castrated monkeys did not bleed microscopically or macroscopically during or after the injection of the anterior lobe extract. The ovaries of the monkeys in which bleeding was produced by the treatment showed no ripe follicles or corpora lutea but there was some difference in the ovaries, as shown by experiments in which the follicles were larger in the ovaries removed after the injections than in the control ovaries. This experimental menstruation-like bleeding was similar to that found in normal monkeys where regular menstruation may occur without rupture of a follicle or presence of a corpus luteum. The uteri from the positive cases showed bleeding from an interval stage of the endometrium. A castrated immature monkey, which did not bleed following injections of hypophysis extract, showed menstruation-like bleeding subsequently after a course of injections with follicular hormone. An immature monkey treated with a sub-effective dose of hypophysis extract and then spayed, showed bleeding after removal of the ovaries. Bleeding which normally follows treatment with hypophysis extract was postponed by injections of follicular hormone. It is assumed from the above experiments that the experimental menstruation-like bleeding results from an alteration of the endometrium which occurs when the effect of follicular hormone is removed.

—Author's Summary.

Secretory cells in the midbrain of the European minnow (Phoxinus laevis L.). Scharrer, E., J. Comp. Neurol. **55**: (No. 2). 1932.

In the midbrain of Phoxinus laevis L. (Cyprinidae, Teleost.) a group of cells is to be found which sometimes produce vacuoles of a colloid-like nature in their cytoplasm. They are to be compared with the cells of internal secretion in the diencephalon of fishes described in earlier papers.—Author's Abst.

Reaction of non-gravid human uterus to extracts of posterior lobe of hypophysis (Die Reaktion der nicht schwangeren menschlichen Gebärmutter auf Hypophysenhinterlappenextrakte). Schultze, G. K. F., Zentralbl. f. Gynäk. **55**: 3042. 1931.

Schultze measured the contractile capacity of the uterus (spontaneous motion) by injection of the uterine cavity with lipiodol, and recorded the results by manometer. He then injected posterior pituitary extract intravenously and observed the activity of the uterus by manometer and by the roentgen-ray. The body of the uterus contracted, bringing about a narrowing of the upper portion of the uterus while the lowest portion of the uterus and the canal dilated. The reaction of the uterus was typical for the different menstrual phases. The strongest contractions to pituitrin were obtained from the twentieth day of the cycle until 24 hours before the onset of the flow. The weakest reaction was obtained six days after menstruation. From the fourteenth day after menstruation there is a gradual increase in the force of the uterine contraction following intravenous injection of posterior pituitary extract. The effect of the oxytocic occurs about one and a half minutes after completion of the injection. There is a preliminary fall in the mercury manometer and then a gradual rise. Uncomfortable symptoms such as feeling of anxiety, headache, pallor and strong pupillary dilatation occurs after the injection.—L. Goldstein.

Roentgenologic measurements of the size of the sella turcica in infancy (Zur Roentgenologischen Messung der Sella Grosze im Sauglingsalter). Schulze, E., Arch. f. Kinderh. **93**: 173. 1931.

The author studied the sella turcica in the age group not covered adequately by either Haas or Sartorius and gives the average figures obtained in infants under one year of age. He confirms the findings of the other investigators in that the sella turcicas of female children above 2 years of age are larger than males of corresponding age.—M. B. G.

A cytological technique for the study of the anterior lobe of the hypophysis. Severinghaus, A. E., Anat. Rec. **53**: 1. 1932.

A rapidly increasing mass of experimental evidence points to a wider participation of the anterior hypophysis in the physiology of the organism. If we are to understand these phenomena, a more careful cytological analysis of the gland is necessary. Any technical procedure to be useful must meet the following requirements: (1) A sharp differentiation of the basophilic and acidophilic granules in the same preparation. (2) A separation of the granular mitochondria from the acidophilic granules. (3) The possibility of demonstrating the Golgi apparatus in the stained preparations. A technical method is outlined which involves a Champy fixation, potassium-dichromate mordanting, acid-fuchsin staining so differentiated that the mitochondria stand in sharp contrast to the acidophilic granules, and a counterstain, obtained by combining acid violet, methyl green, and alcohol, which is more specific for the difficult-staining basophilic granules of certain lower mammals. The method has been successfully used in this laboratory and in several others to which it has been communicated for the study of the anterior pituitary, thyroid, and other epithelial structures in the amphibians, the rat, mouse, guinea-pig, rabbit, and monkey.—Author's Abst.

Embryonic epithelial rests in the pituitary. Susman, W., Brit. J. Surg. **19**: 571. 1932.

In a series of 230 pituitaries removed at routine post mortem examinations 71, or 30%, contained epithelial embryonic rests. An analysis of these 71 cases showed that squamous rests alone occurred in 32 glands, primitive epithelial rests in 29, and primitive glandular rests in 3. In only 7 of the 71 glands were there more than 1 of the 3 types of rests present. The commonest site was in the capsule of the anterior pituitary; the infundibulum and pars intermedia had a slightly lower incidence. Two or more parts of the glands were involved in 15 cases. Few rests occurred in subjects under 20 years of age, although this age group made up 17% of the total series.—Author's Abst.

The absence of gonad-stimulating hormone in the urine and blood of patients with pituitary tumors. Watts, J. W., Proc. Soc. Exper. Biol. & Med. **29**: 396. 1932.

In 6 patients with various acromegalic features and symptoms, 5 patients with chromophobe adenoma of the pituitary and in 3 patients with possible pituitary adenoma, no gonad-stimulating hormone could be demonstrated in either blood or urine. Immature rats were used for the assays.—M. O. L.

The so-called cerebral type of adiposogenital dystrophy (Lawrence-Biedl syndrome) (Uber die angeborene sogenannte zerebrale Form des Dystrophia adiposogenitalis [Lawrence-Biedlsches Syndrom]). Willi, H., Jahrb. f. Kinderh. **133**: 12. 1931.

The author reports three cases of this condition. The first two are in a brother and sister whose parents were related by consanguinity and who presented the picture of adiposogenital dystrophy, syndactilism, mental dullness and visual disturbances due to macular defect in both and retinitis pigmentosa in the girl. They both had low basal rate, low specific dynamic action and large sella turcica. The third case is that of a man of 22 years of age who had been seen and reported 10 years ago by Denzler as having a typical Lawrence-Biedl syndrome, characterized by adiposogenital dystrophy, polydactilism, retinitis pigmentosa and dull mentality. His obesity increased with age. His beard began to grow at 18 years of age. Examination by Willi in 1930 revealed an obese man who appeared much older than his 22 years, who had marked growth of hair on his scalp, lower extremities, pubic and axillary regions and abdomen. The external genitalia were of normal adult size and appearance. His voice was masculine. Vision was poor and retinitis pigmentosa and nystagmus were present. The basal metabolic rate was minus 17.5 and the specific dynamic action 12. The sella turcica was large on x-ray examination. Sugar tolerance was normal.—M. B. G.

Hypophysis and sleep (Hypophyse und Schlaf). Zondek, H. and A. Bier, Klin. Wchnschr. **11**: 760. 1932.

In the medulla oblongata during sleep the authors found an increase in bromine of from 0.38 mgm. per cent to 0.61 mgm. per cent. In the hypophysis during sleep there was only 5-7 mgm. per cent of bromine, while normally there is about 15-30 mgm. per cent. The injection of the extract from the hypophysis (4 cc. of the bromine-hormone) caused great drowsiness and fatigue. Tetra-brom-desiodothyroxine also had the same effect, but did not last so long. Yet 1 mgm. of this bromine-thyroxine was entirely efficacious for man. Dogs were akinetic after an injection of a larger dose applied intravenously or in the cisterna. An injection of 20 mgm. sodium bromide had no effect.
—E. Kodicek.

The hormone of the pars intermedia of the hypophysis. The reddening of the Phoxinus laevis as test (Hormon des Zwischenlappens der Hypophyse. Die Rotfarbung der Elritze als Testobjekt). Zondek, B. and H. Krohn, Klin. Wchnschr. **11**: 405. 1932.

After the injection of the extract of the pars intermedia (Intermedin) an intensively purple color appeared between the fins of the Phoxinus laevis (a small fresh-water fish of Central Europe). The phoxinus unit is the smallest dose, which calls forth a purple color between the fins of 3-5 fishes. This reaction of the erythrophores is specific, no other hormone and no other substance tested can call it forth. The reaction of melanophores and xanthophores of the same fish is not specific, also the reaction of the melanophores of the frog is not specific.—E. Kodicek.

Contraction and evacuation of the gall bladder of the rabbit produced by cholecystokinin. Walsh, E. J., Am. J. Physiol. **100**: 594. 1932.

The gall bladder of the rabbit has been seen by direct vision to contract and evacuate via the cystic duct under the influence of cholecystokinin. Photographs have been made. Similar evidence of evacuation of the viscus has been obtained by analyzing the common duct bile for methylene blue (15 hours after administration) before and after the injection of cholecystokinin. The gall bladder of the rabbit does not contract with sufficient force to evacuate the larger portion of a viscous brominated oil placed within its lumen artificially, which is known to be evacuated in the cat and dog.—Author's Abst.

The action of insulin on vagus excitability (Azione dell'insulina sull'eccitabilitá del N. vago). Barone, V. G., Arch. di fisol. **29**: 394. 1931. Abst., Chem. Absts. **26**: 1663.

Intravenous injections of insulin cause in dogs a lowering of the threshold of vagus excitability. This is not related to the change in blood sugar.

Relation of sugar content in diabetic urine to the daily urine quantity and its specific gravity (Zur Frage der Bestimmung des Zuckergehaltes im Urin bei Diabetes nach der Quantität des Urins in 24 Stunden und nach seinem spezifischen Gewicht). Breitmann, M., Endokrinologie, **7**: 369. 1930.

The author predicts the quantity of sugar on a basis of specific gravity and urine volume for a 24-hour period.—B. C.

Acetylation of crystalline insulin. Charles, A. F. and D. A. Scott, Tr. Roy. Soc. Canada, **25**: 187. 1931.

Crystalline insulin in acetic acid solution, treated with acetic anhydride, loses 98% of its activity. The product is insoluble in acid but soluble in alkali; it contains 7.0% of combined acetyl groups, and 6.5% of acetyl groups as adsorption or addition products. The combined acetyl groups are probably attached to hydroxyl groups of the insulin molecule, since they are released by treatment with dilute alkali, and the product regains 25% of the activity of the original insulin.—D. L. Thomson.

Further studies of the effect of insulin on the amino-acid content of blood. Daniels, A. C. and J. M. Luck, J. Biol. Chem. **91**: 119. 1931.

Insulin was administered by subcutaneous injection to 10 adult human subjects. Seven others, who served as controls, received injections of 0.9% sodium chloride. The observations of Luck, Morrison, and Wilbur on the reduction of the amino-acid concentration in the blood of insulinized subjects were confirmed. The mode of action is discussed.—Authors' Summary.

The direct action of different substances on the endocrine activity of the pancreas (Action directe de diverses substances sur la sécrétion endocrine du pancréas). Foglia, V. G., Compt. rend. Soc. de biol. **108**: 500. 1931.

Methylene blue, secretin, posterior lobe powder, pilocarpine, ergotomine tartrate, acetylcholine, and nicotine were injected into the blood of dogs. None of these influenced the internal secretion of the pancreas.—J. C. D.

Regulation of insulin production (Über die Regulation der Insulinabgabe). Grafe, E., Med. Klin. **28**: 468. 1932. Abst., J. A. M. A. **98**: 2327.

The author shows that the regulatory system of insulin production is much more complicated than it appears at first. According to the law of the double or threefold security, which obtains in nearly all important metabolic processes, there are at least three interacting mechanisms. The superior and the one with the most delicate function is the central nervous system. There is probably a center in the thalamus, which responds directly to the fluctuations in the blood sugar, and which according to need sends its impulses by way of the vagus directly to the islands of Langerhans. In addition to this the sugar, like a hormone, also acts directly on the production centers of insulin. Fluctuations in the activity of the suprarenals likewise act directly on the insulin production. Whether the external secretion of the pancreas also exerts a retalatory influence on the insulin production has not been definitely established as yet, and it is considered improbable.

The effect of various organs on the acetone content of the blood in phlorhizin and pancreatic diabetes. Himwich, H. E., W. Goldfarb and A. Weller, J. Biol. Chem. **93**: 337. 1931.

The acetone metabolism of organs in situ was studied in 12 depancreatized and six phlorhizinized dogs. The liver was found to be the chief site of acetone production (27 of 29 experiments); while muscle and the organs drained by the portal vein liberated acetone bodies in 18 experiments, and removed that substance in 24 others. These results indicate that the acetone excreted by the kidneys and lungs is the algebraic sum of the actions of the various organs.
—H. E. Himwich.

Initial fall in blood sugar after pancreatectomy (Über die anfängliche Blutzuckerabnahme nach Pankreasexstirpation). Horsters, H., Arch. f. exper. Path. u. Pharmakol. **160**: 692. 1931. Abst., Physiol. Absts. **17**: 50.

Fairly often during and after complete pancreatectomy in dogs a fall in blood sugar may be observed, the extent of which partly depends upon the previous nutritive condition of the animal. This is considered as possibly due to insulin being expressed from the pancreas during the operation, escaping by way of the pancreatico-duodenal vein into a liver poor in glycogen, and thence into the general blood stream, or else escaping by way of the lymph channels direct to the blood via the thoracic duct, or else as being due to disturbance of the nervous sugar relation as a result of the operative trauma.

Extraction of insulin and stability of various preparations. Jephcott, C. M., Tr. Roy. Soc. Canada, **25**: 183. 1931.

The extraction of insulin from beef pancreas is best made with hydrochloric acid, 0.125-0.33 N, in 60-80% ethyl alcohol at 38° C. for two hours with shaking; in this way from 3,000 to 3,500 units can be obtained per kilo of pancreas. Purified insulin added to minced pancreas is not well recovered by this technique, but crude material treated in the same way may be quantitatively recovered.—D. L. Thomson.

Glucose-insulin therapy in cardiac insufficiency (La glucosa-insulinoterapia en la insuficiencia cardiaca. Sus fundamentos, su tecnica y sus resultados). Joselevich, M., Semana méd. **2**: 2010. 1931. Abst., Chem. Absts. **26**: 1663.

Glucose plays an important rôle in the nutrition of the heart and its utilization is increased by insulin. In cardiac insufficiency, a disturbance of sugar metabolism is supposed. The results of the treatment are not convincing.

Physiological studies of insulin. Hyperglycemic action of the blood of a diabetic dog. Kepinov, L. and S. Petit-Dutaillis, Arch. internat. de Physiol. **34**: 58. 1931. Abst., Rev. belge sc. med. **4**: 155.

When the blood of a diabetic dog is transfused to a normal dog we get an increase in blood sugar. The glycemic curve obtained in these experiments shows two peaks, one appearing immediately after transfusion which is undoubtedly due to the transfused hyperglycemic blood, and the other appearing only after a fairly long time. This hyperglycemia cannot be interpreted as being caused by the injection of the blood for if the transfusion is normal there is no change in amount of blood sugar in the receiver. This forces us to the conclusion that the blood of the diabetic dog contains a substance capable of causing hyperglycemia. The hyperglycemia is even more noticeable when the experiments are carried out on partially depancreatized animals, whose hyperglycemia is no longer counter-balanced by a large amount of insulin. The increased blood sugar is obtained even after insulin injections have reduced the blood sugar of the diabetic dog to normal. A substance possessing a slight hyperglycemic power has been isolated. The authors conclude from these experiments that diabetic hyperglycemia is due not only to absence of insulin but also to the presence of a hyperglycemic factor.—Translated by J. Gagnon.

Effects of prolonged action of insulin on the hyperglycemic power of diabetic blood (Effets de l'action prolongée de l'insuline sur le pouvoir hyperglycémiant du sang diabétique). Kepinov, L. and S. Petit-Dutaillis, Compt. rend. Soc. de biol. **108**: 626. 1931.

Blood from a diabetic dog produces a marked hyperglycemia when introduced into a depancreatized dog kept in normal condition by a small pancreatic graft. If a depancreatized dog is kept non-diabetic by insulin for four or five days, his blood no longer has this hyperglycemic power.—J. C. D.

Changes in serum protides during diabetes mellitus (Modifications des Albumines du Sang au cours du Diabete Sucre). Labbe, M., and R. Boulin, Presse méd. **39**: 1725. 1931.

Two hundred and twelve determinations were made on 100 patients during a period of two years, by the method of Piettre and Vila. Sixty-eight per cent of the cases, without complications, showed increases in the serum albumin, giving a mean value of 6.18%. The globulin fraction was increased only in 24% of the cases, and the mean value was normal—2.90%. The albumin to globulin ratio was increased in 58% of the cases, with a mean value of 2.32. The total protid was increased in 61% of the cases, the mean value being 9.3%. A greater number of cases with malnutrition showed high albumin values. The increases in albumin and in albumin to globulin ratio disappear during coma, and also under insulin therapy as the blood sugar values return to normal. Authors postulate that these changes are due to overproduction of albumin caused by dysfunction of the liver.—J. M. Looney.

Blood phosphorous in diabetes (Le phosphore sanguin dans le diabètes). Labbe, M. and M. Fabrykant, Compt. rend. Soc. de biol. **108**: 615. 1931.

The phospholipids and other forms of phosphorous were followed in five diabetics without emaciation and in six with emaciation. In the former, the phosphorous was normal. In the latter it varied markedly and irregularly. —J. C. D.

Diagnosis and treatment of diabetic coma. Lemann, I. I., South. M. J. **25**: 411. 1932.

Four cases are cited. One simulated diabetic coma but was due to intracranial hemorrhage, one was diabetic coma but without ketosis, and the two others showed evidence of appendicitis but were relieved by insulin.—J. C. D.

The influence of insulin on the motility of the urinary bladder (dog). Lindquist, J. L., Am. J. Physiol. **100**: 1. 1932.

Subcutaneous injection of insulin causes an increase in motility and tone of the unanesthetized female dog's urinary bladder. Micturition with or without convulsions may occur at the height of the hyperactivity following insulin. The recorded increases in bladder activity were not due to changes in intra-abdominal pressure. The effect of dextrose administered intravenously on insulin hyperactivity is not constant, but inhibition is frequently noted. In this series of dogs the majority showed a considerable degree of urinary bladder motility, prior to injection of insulin.—Author's Summary.

Effect of excessive insulin on the pancreatic islets of young rats. McJunkin, F. A. and B. D. Roberts, Proc. Soc. Exper. Biol. & Med. **29**: 893. 1932.

Insulin administration to rats caused inhibition of the islet cells. The growth of the animals continued normally.—M. O. L.

Insulin fattening: late results in sixty-three cases. Nichol, E. S., South. M. J. **25**: 405. 1932.

Sixty-three patients, all underweight and suffering from a variety of ailments but with unimpaired carbohydrate mechanism, were given a course of insulin treatments and a rich diet. Forty-eight gained from 5 to 30 pounds in a short time. Forty-two of these have been followed. Twenty-three held their gains in weight for 3 months or less, eight for 6 months, seven for one year, three for 3 years, and only one for 4 years.—J. C. D.

Accentuation of insulin effect by lipoids (Potenzierte Insulinwirkung durch Lipoide). Suranyi, L. and F. Szalai, Klin. Wchnschr. **9**: 2159. 1931. Abst., Chem. Absts. **26**: 2510.

The hypoglycemic action of insulin injected intravenously into rabbits is enhanced by the addition of an emulsion of cholesterol or lecithin to the insulin. Moreover, if lecithin is added to insulin and the mixture is injected subcutaneously, there is a very marked prolongation of the hypoglycemic phase.

Studies on the physiology of the parathyroid glands; relation of the serum calcium to the serum phosphorus at different levels of parathyroid activity. Albright, F., W. Bauer, J. R. Cockrill and R. Ellsworth, J. Clin. Investigation, **9**: 659. 1931.

From an analysis of 354 simultaneous determinations of serum calcium and serum inorganic phosphorus in patients at varying degrees of hypoparathyroidism and hyperparathyroidism, it would appear that one rises as the other falls to such a degree that their product remains roughly constant. It is pointed out that such a constancy implies a slight reduction of phosphorus at high levels of calcium but a marked increase of phosphorus at low levels of calcium. The question is raised whether this constancy represents the direct expression of a law or whether it is merely a close approximation to some law. In this connection it is pointed out that if calcium and phosphate are precipitated in the bones as secondary calcium phosphate and if the effect introduced by serum protein can be shown to be constant there may be chemical support to such a constancy. The effects of serum protein, the thyroid hormone, the species of organism, the phenomenon of growth and pH on the product of Ca x P are discussed. It is believed that dysfunctions of the parathyroid glands belong to that group of calcium disorders in which the body fluids contain a normal amount of calcium phosphate but in which the relation of the calcium to the phosphate is abnormal. However, at very high levels of calcium a secondary phenomenon occurs. Phosphorus is no longer excreted in the urine and serum phosphorus abruptly rises. This results in a disorder of calcium metabolism where the body fluids contain an increased amount of calcium phosphate and leads to calcium phosphate precipitation in tissues other than bone. The data give no clue as to whether with parathyroid administration the serum calcium rises because the serum phosphorus falls, or whether the serum phosphorus falls because the serum calcium rises. Based on this data alone one supposition is as logical as the other.—Authors' Summary.

Attempt to influence calcium metabolism by roentgen irradiation of parathyroids (Ein Versuch, durch Röntgenbestrahlung der Epithelkorperchen den Kalkstoffwechsel zu beeinflussen). Biedl, A., Med. Klin. **28**: 251. 1932. Abst., J. A. M. A. **98**: 1695.

Biedl reports the clinical history of a girl, aged 19, with osteitis fibrosa of the left hip joint. Since palpation of the parathyroids did not reveal the presence of an adenoma, the author hesitated to resort to a surgical intervention on them, although the increased calcium content of the blood indicated their hyperfunction. Instead he resorted to roentgen irradiation as the nonsurgical method of exclusion. He describes the technic of the treatment, which was given in three series, and states that the effect was entirely satisfactory. The calcium content of the blood decreased and the function of the left hip joint improved to such an extent that the patient was again able to do her work. On the basis of the effects obtained with intensive roentgen irradiation in the reported case, the author recommends this treatment for cases of osteitis fibrosa, whether localized or generalized, no matter whether a tumor of the parathyroids is demonstrable or whether its presence is indicated only by an increased calcium content of the blood.

On the question of the rôle of the parathyroid glands in the pathogenesis of genuine epilepsy (Zur Frage der Rolle der Nebenschilddrüsen in der Pathogenese der genuinen Epilepsie). Brodski, A. O., Wien. klin. Wchnschr. **44**: 707. 1931.

Brodski mentions some of the older European literature dealing with disturbances of physiological chemistry or of endocrine function in patients with epilepsy. He reports four cases of his own in which the parathyroid glands of goats were transplanted into patients. All were adults having frequent and severe seizures. Apparently none presented evidence of lack of parathyroid function. In two of these cases seizures have been virtually absent for the seven months and the seven years, respectively, which had elapsed since the operation. In the other two cases, failure to influence seizures is attributed to the operative technique.—W. G. Lennox.

The physiology of the parathyroid glands. Collip, J. B., Canad. M. A. J. **24**: 646. 1931.

A review dealing with the metabolism, absorption, and excretion of calcium, the relation of inorganic phosphorus to calcium, the internal secretion of the parathyroids, its relationship to vitamin D, and clinical conditions in which calcium metabolism or parathyroid function is disturbed.—A. T. C.

Experimental chronic hyperparathyroidism; osteitis fibrosa produced in rats. Johnson, J. L., Am. J. M. Sc. **183**: 761. 1932.

Thirty-two white rats, aged from 6 to 12 weeks, were injected daily for period of from 10 to 43 weeks with parathormone in doses of from 10 to 20 units. A Steenbock normal rat diet was given. Uninjected litter mate controls remained well, whereas the injected animals developed, without exception, muscular weakness, hypotonia and skeletal lesions characteristic of osteitis fibrosa osteoplastica (von Recklinghausen), namely, a lacunar resorption of bone with softening and deformity, bending and multiple fracture. The cortex and marrow of these bones were largely replaced by fibrous connective tissue containing numerous giant cells, and new bone osteoid tissue was also in evidence in numerous cases. Chronic hyperparathyroidism produced in rats by repeated injections of parathormone leads to bone changes which justify a diagnosis of osteitis fibrosa. These experiments support the conclusion that the cause of clinical osteitis firbosa osteoplastica (von Recklinghausen) is an excess of the parathyroid hormone.—Author's Summary.

Experimental chronic hyperparathyroidism; osteitis fibrosa produced in puppies. Johnson, J. L., Am. J. M. Sc. **183**: 769. 1932.

The experimental production in puppies of a state of chronic hyperparathyroidism is reported (35 cases) and descriptions are given of the gross, roentgenologic and microscopic abnormalities resulting therefrom. This experimental disease, produced with repeated injections of parathormone, is

characterized by skeletal lesions and other abnormalities which correspond closely to those observed in clinical cases of osteitis fibrosa osteoplastica (von Recklinghausen).—Author's Summary.

Experimental chronic hyperparathyroidism; effects of administration of irradiated ergosterol. Johnson, J. L., Am. J. M. Sc. **183**: 776. 1932.

An answer was sought to the question as to the relationship of osteitis fibrosa to those other skeletal diseases, especially rickets and osteomalacia, that are also associated with hypertrophy of parathyroid glands. Metabolic studies of the problem have been reported previously; the results of animal experiments are given here. Irradiated ergosterol, in a dosage of 5 to 60 drops daily, was fed to young, white rats and puppies maintained in a chronic state of hyperparathyroidism by the daily injection of parathormone. These animals were litter mates of others that developed the skeletal lesions of osteitis fibrosa when treated with parathormone alone. The technique of experimentation, the diets and dosage of the parathormone was the same as that previously reported. The outcome was the same, except that the resulting lesions typical of the skeletal abnormalities of osteitis fibrosa were, on the whole, more extensive. Metastatic calcification in the kidneys was also more marked. Whereas vitamin D concentrates effectively protect against rickets or osteomalacia, it is evident from these experiments that they intensify the disease produced by excess of parathyroid hormone. It is, therefore, clear that rickets or osteomalacia differ essentially in pathogenesis from osteitis fibrosa. While the hypertrophy of the parathyroids in conditions of vitamin D deficiency may be compensatory and is certainly a secondary phenomenon, the tumors of parathyroids found in association with osteitis fibrosa are of primary significance. It is recognized, however, that overfunction of parathyroids may occur in the absence of tumors or other morphologic abnormality.—Author's Summary.

Removal of parathyroid adenoma for diffuse lesions and decalcification of bones (Ablation d'adénome parathyroïdien pour lésions diffuses du squelette avec décalcification évolutive; grande amélioration). May, E. and J. A. Lièvre, Bull. et mém. Soc. méd. d hôp. de Paris, **47**: 1808. 1931.

The patient was a male, 45 years of age, who had had an attack of renal colic four years before the onset of the complaint referable to the osseous system. His osseous symptoms were extreme pain in and sensitiveness of the bones, spontaneous fractures and tumorfaction. There were gastric crises and constipation. Tachycardia was also complained of. The patient showed no hypercalcemia and the blood phosphorus was 2.5 mgm. per 100 cc. of blood. Roentgenological examination disclosed very intense decalcification, especially marked in the pelvis. A parathyroid adenoma was removed with immediate amelioration of the symptoms, but the patient had a severe attack of tetany which, however, cleared up under therapeutic procedures.—H. L. Jaffe.

The clinical aspect of disturbances of the parathyroid glands. Meakins, J. C., Canad. M. A. J. **24**: 654. 1931.

The author concludes that, clinically, two conditions are identifiable with disturbed parathyroid function, the first being parathyroid tetany due to a hypoparathyroidism characterized by a low serum calcium, a positive calcium balance, and great hypertonicity and excitability of the neuro-muscular system. On the contrary, there is generalized osteitis fibrosa, a condition of hyperparathyroidism in which there is a high serum calcium, a negative calcium balance, and a tendency to hypotonicity and hypoexcitability of the neuro-muscular system, a pronounced rarefaction of the bones, and a resorption of the corticalis and original spongiosa, this being in striking distinction to the cessation of calcification characteristic of osteomalacia and rickets.—A. T. C.

Pineal extract and calcium metabolism (Action de l'extrait pineal sur la calcémie). de Candia, S., Rev. franç. d'endocrinol. **9**: 23. 1931.

Series of investigations on (a) normal humans, by buccal and parenteral administration, (b) dogs by intravenous injection, (c) humans by intravenous injection and checked by gonadal administration were made. Results indicate that the pineal has to do with calcium metabolism as determined by the blood calcium, especially as related to calling out reserves from storage depots, one

of which may be in the gland itself. Studies on calcium elimination indicate that the gland is not concerned with fixation of calcium in the various depots. —B. C.

On the endocrine secretion of the spleen (Ein weiterer Beitrag zur Frage der inneren Sekretion der Milz). Flaum, E., Wien. klin. Wchnschr. **44**: 1044. 1931.

In former experiments Lauda and Flaum found that rats infected with Bartonella and then splenectomized become ill with symptoms of Bartonella anaemia. The control, infected but not splenectomized, did not show any signs of illness. Rats in parabiosis did not become ill, if either of the pair had a normal spleen. To splenectomized rats Brüda and Pfeiffer could transplant a tumor of mice, which does not grow in normal rats. In a new experiment the author also shows the relation of spleen and marrow. In normal rats after splenectomy, Howell-Jolly corpuscles appear in erythrocytes. In parabiotic animals the splenectomized ones did not show this sign of higher blood regeneration, if they were connected with a normal rat, but Howell-Jolly corpuscles appeared after splenectomy of the other rat.—E. Kodicek.

A "lipoid" extract of spleen that prevents Bartonella muris anemia in splenectomized albino rats. Perla, D. and J. Marmorston-Gottesman, Proc. Soc. Exper. Biol. & Med. **29**: 987. 1932.

A "lipoid" extract of the spleen was prepared which protects adult albino rats of carrier stock in a large percentage of instances against Bartonella muris anemia following splenectomy. One cc. of extract (corresponding to 100 grams of fresh spleen) is injected daily intraperitoneally in divided doses for a month. It is suggested that the extract contains a specific hormonal substance.—Author's Summary.

The influence of the thymus on growth and the extraction of an effective thymic material thymocrescin (Der Einfluss der Thymus auf das Wachstum und die Herstellung enes wirksamen Thymusstoffes Thymocrescin). Asher, L., Endokrinologie, **7**: 321. 1930.

Following a review of certain investigations dealing with the function of the thymus, the author contends that the results of extirpation of that gland cannot be conclusive in settling the question of its function. More significant would be the effects of overthymoidization, especially when the foodstuff given is poor in growth-promoting substances. In his experiments he chose one that was free from growth-promoting vitamins. When fed a mixture of a rickets-producing diet together with substances from which the growth-promoting factor was absent, the growth of young white rats was greatly interfered with. As an introductory statement, he says that if normal young rats are injected with an aqueous extract of thymus, or have many small pieces of the gland implanted in them, and are furthermore well fed with thymus and a diet favoring it, the growth is truly extraordinary. Returning to the critical experiments, the control animals fed on a richitic diet had rickets badly. Those similarly fed but thymus injected show no sign of rickets, even when examined microscopically. This effect of thymic injection is not, however, unique, for the same can be obtained by feeding muscle. There remains, however, a noteworthy difference between the effect of the thymic feeding and the feeding of muscle, in that in the former growth was incomparably greater than in the latter. The experiments described deal not only with the effect of injected thymus extract, but describes in detail a method of extracting purified specific growth-promoting substances which the author names thymocrescin. This is truly a growth-promoting substance, especially when the food is unfavorable. It has, furthermore, the effect of causing a decrease in calcium elimination in growing rats, a phenomenon associated with normal vertebrate growth. —R. G. Hall.

The weight of the thymus gland in health and in disease. Boyd, Edith, Am. J. Dis. Child. **43**: 1162. 1932.

In spite of the repeated demonstration that the thymuses of healthy, well-nourished children are prominent and average 20 gm. or more in weight and that wide thymic shadows on roentgenograms of infants' chests are common, the belief persists that these findings represent a constitutional susceptibility

to death from trivial causes, i.e., status thymicolymphaticus, and account for most respiratory symptoms of infancy. Because of the tenacity of these misconceptions, the author has undertaken to demonstrate their fallaciousness first by an elaborate review of the normal growth phenomena of the thymus and of its reaction to disease and inanition, second by a graphic presentation of these phenomena from additional data, and third by a comparison of the statistics from the new data with those obtained by previous workers. This analysis has again demonstrated that while the mean thymus weight in normal persons is about 2 gm. more than the median, both increase rapidly in the first months of life, double their birth size by 2 years and triple it by 11 years; then both decrease slowly to about birth size in senility. This general progression holds for data from the United States, Germany, France, Sweden and England. A graphic presentation of Hammar's data indicates that the parenchyma decreases sufficiently after puberty to lower the total weight of the thymus even though the connective tissue and fat are increased in amount. At all ages the variability of the weight of the thymus is high. This dispersion has been estimated both by interquartile range and by coefficient of variation. Since the spread of weights above the median weight is greater than that below it, the interquartile range has been used to construct a graphic standard of normal variability, instead of the standard devitation or a related statistic. When illness has lasted longer than twenty-four hours, the weight of the thymus is reduced regardless of the cause of death, with the exception of tumors of the thymus, leukemia and exophthalmic goiter. This involution is probably part of the general involution of most organs found in inanition, but the thymus, like the subcutaneous fat and lymphoid tissue, reacts markedly and rapidly, so that all three are significantly decreased in most illnesses lasting more than twenty-four hours. The concept of a pathologic state arose from misconstruing the normal prominent thymus and lymphoid tissue for a constitutional abnormality and vice versa, the involuted, inconspicuous thymus of inanition being misconstrued for the normal.—R. G. H.

The change of status lymphaticus. Kemp, W. N., Bull. Vancouver Med. Ass. **7**: (April). 1932.

The author reports two further cases of sudden death in infants showing at autopsy generalized lymphadenopathy including enlargement of the thymus. He emphasizes the prevalence of that condition in the Pacific Northwest and theorizes plausibly to the effect that the essential factor in the disorder is insufficiency of the adrenal cortex.—R. G. H.

Thymus fremitus as an indication for roentgenotherapy. Wade, A. E., Am. J. Dis. Child. **43**: 1641. 1932.

Tactile fremitus elicited by the pressure of the finger-tip over the sternum is a valuable sign in differentiating those cases of stridor in infants which can be relieved by roentgenotherapy from those cases in which the stridor is not so satisfactorily relieved, whether the thymic shadow is enlarged or normal. This sign was present in 100% of the cases of stridor in which relief was obtained by roentgenotherapy and absent in 100% of the cases in which no relief was obtained by such therapy. The fremitus is best noted by lightly placing three or four finger-tips over the sternum during the presence of stridor. A vibration can be felt, and, as the fingers move to right and life, up and down, over the manubrial region, an outline can be forecast of the shadow later observed upon the roentgenograms. This sign has been dependable as an indication that roentgenotherapy will relieve the stridor, whether the anteroposterior shadow of the thymus is large or not. It reveals that there is density beneath the sternum sufficient to transmit the vibrations.—M. B. G.

The response of Bufo larvae to different concentrations of thyroxin. Allen, B. M., Anat Rec. **54**: (No. 1). 1932.

1. Tadpoles of Bufo halophilus at a stage well prior to the rapid changes of metamorphosis were exposed to thyroxine solutions ranging in concentration from 1:2,000,000 to 1:1,000,000,000 (5000 times more dilute). 2. No response of any portions is observed at solutions of thyroxine of concentrations less than 1:200,000,000, and in this solution the response during the time limits of these experiments is very slight. 3. The different parts studied may be arranged in order of responsiveness to lower concentrations of thyroxine as

follows: (1) alimentary tract; (2) hind limbs; (3) change in color of gall bladder. Tongue growth. Loss of horny jaws; (4) reduction in length of tail. Reduction in length of body. 4. The speed of response is in proportion to the concentration of the thyroxine solution used up to certain maximum limits, beyond which greater concentrations cannot give greater rate of development. 5. The influence of thyroxine is proportional to the age of the tadpole, being slight in the young periods beginning with tail-bud stage and becoming far more pronounced in the period of 20 mm. total length.—Author's Abst.

"Myxedema heart" without evidence of cardiac insufficiency. Ayman, D., H. Rosenblum and M. Falcon-Lesses, J. A. M. A., **98**: 1721. 1932. Abst., A. M. A.

In two cases of "myxedema heart," observed by the authors, both patients had clinical, roentgenographic and electrocardiographic manifestations which were characteristic of the condition as described by previous workers and which became normal after adequate treatment with thyroid. Enlargement of the heart and its return to normal with adequate thyroid treatment is stressed as the one diagnostic feature of "myxedema heart," since the other abnormalities are usually found in all cases of myxedema. Factors other than thyroid medication may decrease the size of the heart during treatment for myxedema. Little, if any, evidence of heart failure was found in either of the cases reported, and hence it is believed that cardiac insufficiency, although sometimes found, is not characteristic of "myxedema heart." The suggestion is made that "myxedema heart" may be more common than is usually supposed, and therefore the need of securing serial teleroentgenograms of the heart and electrocardiograms before and during the treatment of every patient with myxedema is indispensable to exclude the possibility of the presence of "myxedema heart."

The influence of intravenous injections of thyroxine on blood-level of iodine and on the secretion of iodine in the urine of man (Über den Einfluss der intravenösen Thyroxininjektionen auf den Blutjodspiegel und die Harnjodausscheidung bei Menschen). Boe, J. and W. Elmer, Klin. Wchnschr. **11**: 721. 1932.

After injection of 2 mgm. thyroxine the authors found an increase of the alcohol-soluble iodine in the blood. The alcohol-insoluble part did not change. After 2-3 hours there was a normal blood-level of iodine. The curve of iodine content of the urine was parallel with that of the blood. After 24 hours there was a normal level of iodine in the urine. Only one-fifth of the iodine was secreted by the kidneys.—E. Kodicek.

Some practical aspects of hypothyroidism. Breckinridge, S. D., Am. J. Obst. & Gynec. **23**: 871. 1932.

The abstracts of 25 case reports are submitted, in 24 of which slight to moderate hypothyroidism existed in company with other symptoms. In 79% of the patients that remained under observation for a sufficient period to justify conclusions, complete relief of symptoms followed thyroid medication. In the remaining 21% improvement was sufficiently marked to make other treatment unnecessary. In the gynecologic group, menorrhagia was the usual presenting symptom. During the period in which these patients were seen, only one patient was seen in whom the picture of menorrhagia, with shortening of the intermenstrual interval, was accompanied by hyperthyroidism. It is concluded that slight to moderate degrees of hypothyroidism may be very important causal factors in a number of gynecologic and obstetric conditions. These include amenorrhea and, more frequently, menorrhagia and probably include abortion, miscarriage, premature labor, and death of the fetus. Hypothyroidism is one of the more frequent causes of menorrhagia and metrorrhagia and should be excluded before resorting to the curette, radium, x-ray, or abdominal section.—Author's Abst.

The management of toxic goiters. Brenizer, A. G., South. M. J. **25**: 251. 1932.

A brief discussion is given of the results of 2,500 thyroidectomies. Among other points, the author mentions the undesirability of using iodine postoperatively and the very bad risk represented by exophthalmic patients, with severe gastro-intestinal symptoms.—J. C. D.

Are seasonal variations of thyroid gland dependent upon corresponding variations in anterior pituitary? Byars, L. T., Hilda Friedman, W. J. Siebert and L. Loeb, Proc. Soc. Exper. Biol. & Med. **29**: 797. 1932.

Seasonal variations corresponding to those which have been observed in the mammalian thyroid gland could not be established in the case of the anterior pituitary of cattle. While these investigations do not absolutely exclude the possibility that cyclic changes of a more subtle kind may occur in this organ, they render them at least very improbable. It is, therefore, probable that the seasonal variations in the thyroid gland are not determined by primary changes of an annual cyclic character in the anterior pituitary, but that they are due to climatic differences during the seasons of the year, and that the effects of these differences are transmitted to the thyroid gland either directly from the periphery or indirectly through the mediation of other organs. The seasonal changes in the thyroid gland apparently correspond to differences in the need of thyroid hormone at different times of the year. Owing to a diminished need of thyroid hormone on the part of the organism during the summer months, after extirpation of the greater part of the thyroid the remaining part of the gland responds less actively with compensatory hypertrophy during this time of the year.—Authors' Summary.

Treatment of exophthalmic goiter and hyperthyroidism by intravenous injections of sodium fluoride (Tratamiento del bocio exoftalmico y del hipertiroidismo por las inyecciones intravenosas de fluoruro de sodio). Goldemberg, L., Semana méd. **2**: 1833. 1931. Abst., Chem. Absts. **26**: 1663.

Thyroxine is precipitated by 10 parts NaF. Doses of NaF by mouth are often not well tolerated. A 2.5% solution in doses up to 350 mgm. NaF is tolerated without shock, when given intravenously. Doses higher than 0.1 gram cause a short intense abdominal pain. Polyuria may be observed. The treatment starts with 3 cc. daily, goes gradually up to 6 cc. and is reduced again to 4, which dose is continued until 15-20 injections are given. The results are slow, but they persist.

Results of feeding thyroid glands of various types of vertebrates to tadpoles. Gunthorp, H., Physiol. Zoöl. **5**: (No. 3). 1932.

Various kinds of thyroid were fed to tadpoles of three different species, the primary object being to ascertain whether or not there was any correlation between the amount of iodine contained in the thyroid and the rate of metamorphosis of the tadpoles. Regardless of the species used, the results obtained led to the classification of the foods into three groups. Those causing relatively slow development included calf, raw beef, cooked beef, pig, and flounder thyroids. Those causing rapid development were dog, human, buffalo, and bear thyroids and two commercial thyroid preparations. Those fed cat thyroid fell between these two extremes. The correlation between the amount of iodine consumed and the rate of development was close with few exceptions. In fact, if equal amounts were fed, the food containing the most iodine usually produced the most rapid metamorphosis regardless of the source. Parallel experiments carried on under two different temperatures indicated that a higher temperature accelerated the rate of metamorphosis, but this factor had no effect on the results obtained from the different foods. Parallel experiments performed in two amounts of water showed that those kept in a smaller amount developed faster, but there was no indication of a differential effect when the different thyroid foods were given.—Author's Abst.

Abdominal pain due to hypothyroidism. Hinton, J. W., J. A. M. A. **98**: 1702. 1932. Abst., A. M. A.

The author calls attention to hypothyroidism as a factor in producing abdominal pain, and emphasizes that patients giving negative roentgen evidence of changes in the gastro-intestinal tract, the gallbladder and the genito-urinary region, as well as negative results in the other laboratory procedures, may in a small percentage of cases be suffering from hypothyroidism; in this group with negative roentgen observations a metabolic determination should be done before any treatment is instituted or before the patients are submitted to an exploratory laparotomy, as occasionally a diagnosis will be established and the symptoms relieved with thyroxine and thyroid extract, the patient being saved a

needless operation. There seems little question that, in the past, probably quite a few exploratory procedures have been undertaken with negative results or at least with symptoms persisting after the operation, in which case the entire trouble was referable to the thyroid gland. The condition is probably due to a hypoperistalsis with a pylorospasm and retention of undigested food in the stomach; after the patient vomits the retained food, or the stomach slowly empties, the symptoms are relieved. The author does not want to leave the impression that all patients with abdominal pain in which the roentgenologic observations are negative are suffering from hypothyroidism, for such is not the case; but if this condition is borne in mind a definite diagnosis can be made in a small percentage of cases, and the individual can be benefited by the proper medication. On the other hand, a patient may have a minus metabolic rate and a definite intraabdominal lesion which will need either medical or surgical treatment. Of course, no benefit could be expected from the abdominal pain by treating the hypothyroidism and neglecting the other condition that is actually causing the pain.

Tubercle-like structure in human goiters. Jaffe, R. H., Arch. Surg. **21**: 717. 1930.

In three cases of nodose goiter and in one case of diffuse goiter with mild hyperthyroidism there were found in the removed thyroid nodular structures composed of epithelioid cells and giant cells which resembled miliary tubercles. The origin of these cells could be traced to the follicular epithelium. The patients showed no other signs of tuberculosis and made an excellent recovery. There was no caseation in these nodules, but much fibrosis about them. In spite of a most careful search, tubercle bacilli could not be demonstrated. The explanation is advanced that the tubercle-like structures are the result of non-infectious focal involutional changes of newly formed and old follicles. These non-tuberculous changes should be separated from true tuberculosis of the thyroid.—Author's Summary.

Effects of thyroid administration on animals with cerebral injury (Effetti della somministrazione di tiroide negli animal cerebro-lesi). Jedlowski, P., Arch. dello Istituto Biochimico Italiano, **4**: 9. 1932.

The experimental researches of the author were suggested by Ceni's observations on the influence of cerebral lesions. Decerbration on chickens has been shown to result in hyperthyroidism. The author investigated the problem whether the tolerance to administered thyroid would be diminished by decerebration. It was found that evidences of intoxication were produced with notably smaller doses of thyroid in decerebrate than in control healthy pullets. Likewise the lethal period was shortened. In decerebrate guinea pigs evidences of toxicity appeared only after more than 20 days. In control animals minimal doses of thyroid caused increase of body weight but in decerebrate animals decrease. With larger doses emaciation followed in both groups but more conspicuously in the decerebrated. The possibility that the diminution of tolerance following decerebration was due to the operative trauma, as such, was excluded. Histologic studies showed that decerebration resulted in no significant alterations in the thyroid and testes but that thyroidization in decerebrated animals resulted in involution of the testes. The results are regarded as demonstrating an influence of the brain of mammals on the endocrine glands. It is suggested that this relationship should receive practical consideration in planning gland therapy or organ transplantation.—G. Coronedi.

A method of estimating the functional activity of the thyroid by means of urine or serum, and studying the relationship between the thyroid and the other endocrine organs. Koh, M., J. Chosen M. A. **22**: (No. 2). 1932.

The author proposes a new method for the direct assay of blood or urine for thyroid hormone. This is based upon the ability of these fluids from normal animals to neutralize the mydriatic effect of atropine. Treating an experimental animal with desiccated thyroid for seven days led to an increase in the neutralizing substance. Conversely, thyroidectomy decreased it. Ten days after the thyroidectomy there was found to be a slight increase in the neutralizing substance, hence, the postulate was offered that the substance is not the thyroid hormone itself. This was confirmed by the failure of thyroid extract or thyroxine directly to neutralize the atropine. The neutralizing substance

was found to increase after removal of the thymus, the parathyroids or the spleen; also after injection of adrenaline. It was decreased by extract of adrenal cortex, insulin, folliculine, prolan, or India ink; likewise as a result of hunger. In cases of exophthalmic goiter and pregnancy, the titre was more than doubled. The substance was found to be easily soluble in water but not in alcohol or ether. It was heat stable at 80° for 30 minutes but destroyed at 100° C. In setting up the test 0.1 cc. of 1% solution of atropine sulphate is added to a graduated series of test tubes of the fluid to be tested, the series running by seven steps from 0.5 cc. to 10.0 cc. After 5 to 10 hours two drops of the treated fluid is instilled into the conjuctival cavity of a cat, the other eye serving as a control. A mydriasis persisting from one-half to four hours indicates the absence of the neutralizing substance. The stated quantity of atropine was commonly found to be neutralized by 4.0 cc. of rabbit urine or 2.0 cc. of human urine. For testing serum, the same quantity of atropine is used in a series running from 0.05 to 1.0 cc. The standard quantity of atropine was found to be neutralized with 0.4 cc. of normal rabbit serum.—Condensed from Author's Abst.—R. G. H.

Studies on the thyroid gland; the physiological activity of iodine in thyroxine and in normal and pathological thyroid glands. Krogh, Marie and Anna-Louise Lindberg, Acta path. et microbiol. Scandinav. **9**: 21. 1932. Abst., Chem. Absts. **26**: 2782.

The biological activity of thyroxine, dried pig thyroid and resected human thyroids on the metabolism of full-grown male guinea pigs has been compared by feeding doses corresponding in each case to 4.5 mgm. iodine per square meter surface every other day for two weeks and measuring daily the resting metabolism at 31-32°. The activity of thyroxine is about two-thirds of that of dried pig thyroid. The iodine content of the human glands varies greatly; in simple goiters between 0.04 and 0.4%, in exophthalmic goiters without iodine treatment between 0.03 and 0.07 and in iodine treated exophthalmic goiters between 0.03 and 0.4%. The dried glands from simple goiters and from exophthalmic goiters successfully treated with iodine brought about an increase in metabolism of nearly the same magnitude as that caused by normal pig thyroids. Glands from non-treated exophthalmic goiters and from iodine treated cases in which the treatment was ineffective, both clinically and histologically, showed a biological activity per mgm. iodine markedly below the normal. The most probable explanation appears to be that in thyroids which are unable to store the hormone but give it off to the blood as rapidly as it is formed the intermediate products between inorganic iodine and the final hormone may make up a significant fraction of the total iodine which probably is not the case in normal glands or colloidal goiters.

Studies on the thyroid gland; experimental hyperactivity of the thyroid gland. Krogh, Marie, Anna-Louise Lindberg and H. Okkels, Acta path. et microbiol. Scandinav. **9**: 37. 1932. Abst., Chem. Absts. **26**: 2783.

Extracts from the anterior lobe of the pituitary injected subcutaneously, into young or full-grown guinea pigs, induce hyperactivity of the thyroid. Peroral administration of the alkaline extract showed no effect. Subcutaneous injection of sex hormone preparations of the anterior lobe of the hypophysis gave perhaps a slight decrease in the standard metabolism, but no structural changes in the thyroid gland. Peroral administration of large doses of dried thyroid or subcutaneous injection of thyroxine solution, daily up to one week, produced a considerable increase in the metabolism, but no change in the thyroid gland.

Exophthalmic goiter and pregnancy (Basedow'sche Krankheit und Schwangerschaft). Küstner, H., Zentralbl. f. Gynäk. **55**: 578. 1931. Abst., J. A. M. A. **96**: 2005.

Küstner asserts that the function of the thyroid during pregnancy is still subject to controversy. His observations on two gravidas, aged 23 and 25, may throw light on the relation between thyroid function and gravidity. Both of them had exophthalmic goiter for years, so severe that one patient had become unable to work and the other had undergone an operation, which had not been successful. The fear that the pregnancy might aggravate the hyperthyroidism proved groundless. At the beginning of the gestation the patients

felt poor and were troubled with hyperemesis, but at about the middle of the pregnancy term they improved markedly. Although the general condition of both women improved, hyperthyroidism still existed, both women carried their fetuses over term and the uterine contractions were weak. These abnormalities are considered the result of the hyperfunctioning of the thyroid, because the action of the thyroid is antagonistic to the function of the posterior lobe of the hypophysis. The author concludes that during pregnancy, especially toward the end of the term, the functioning of the thyroid decreases. In healthy gravidas this does not cause disturbances; in women with hyperthyroidism it has the effect that the hyperfunctioning is partly counteracted and thus their condition improves; in women with hypothyroidism, however, exacerbation is the result.

Comparative activity of the thyroids from male and female pigeons (Zur Untersuchung der vergleichenden Aktivität der Mannchen- und Weibechenschildruse bei Tauben). Larionov, W. T., Endokrinologie, **7**: 23. 1930.

Thyroid tissue from either male or female pigeons gave indistinguishable results when used to produce metamophosis in tadpoles and regeneration of feathers in pigeons.—B. C.

The distribution of iodine in normal and induced hyperthyroid glands. Iodine metabolism (Untersuchungen über den Jodstoffwechsel; ueber die Verteilung des Jods in normalen und jodbehandelten hyperthyreotischen Schilddrüsen). Lunde, G. and K. Wülfert, Endokrinologie, **7**: 327. 1930.

Iodine occurs in the thyroid in three combinations: (a) water soluble, acetone soluble, (b) water soluble, acetone insoluble, (c) water insoluble. The first is probably inorganic, the second is protein and contains the active principle. The water insoluble fraction also contains iodine, which seems to be bound to an insoluble protein. After induced thyreotoxicosis the thyroids were removed and compared with normal structures. Normal—Dry Wt. Av. Factor, 3.7 per 100 gr.; Acetone Sol. Av. W. 5.39; Acetone Insol. below aver. for normals. Experimental—4.8 per 100 gr.; 3.66 per 100 gr. The dry weight factor for the normal is less than for the treated animal; the acetone-water soluble fraction factor is noticeably higher in the normal, while the acetone insoluble fraction factor is lower than normal. The difference in certain pathological cases is still more striking and it is suggested that a study of the gland might have diagnostic value.—B. C.

Exophthalmic goiter in identical twin girls. Neff, F. C., J. Pediat. **1**: 239. 1932.

The author reports what he believes to be the first case in the literature. The children were 11 years of age and resided in an endemic goiter region for 9 years, but there was no familial thyroid history. Prominence of the eyes and enlargement of the neck appeared in one at 8 and the other at 10 years of age. The basal metabolic rate was plus 68 in each. There was a weight loss (insensible perspiration) of 50 gm. in one and of 39 gm. in the other.

—M. B. G.

Basal metabolism during pregnancy in patients with goiter (Der Grundumsatz in der Schwangerschaft und seine Beziehungen zum Kropf und zur Schädigung des Neugebarenen). Niederwieser, V., Monatschr. f. Geburtsch. u. Gynäk. **90**: 401. 1932. Abst., J. A. M. A. **98**: 2256.

In an Alpine region where goiter is endemic, Niederwieser found that in pregnant women the basal metabolism is increased even if they do not have goiter. The average increase is about 15%. The size of the goiter and its consistency have no noticeable influence on the basal metabolism, and the same can be said about the age of the gravida and the number of confinements. However, there is a parallelism between the depth of respiration, which gradually increases with the advancing pregnancy, and the basal metabolism. The specific dynamic action is reduced during pregnancy, and the author thinks that this is due to the morphologic changes in the hypophysis. The goiter exerts no noticeable influence on the course of pregnancy. The thyroidal function of the new-born is influenced neither by the type and size of the mother's goiter nor by her basal metabolism.

Further observations on the parafollicular cells of the mammalian thyroid. Nonidez, J. F., Anat. Rec. **53**: 339. 1932.

The observations on the origin of the parafollicular cells of the thyroid of the dog have been extended to the cat and rabbit. Parafollicular cells in the cat arise as in the dog, but they differ from the corresponding elements in the dog. thyroid in that they do not contain strongly argyrophilic granules in their cytoplasm. Furthermore, they are not quite as large as in the dog. The parafollicular cells of the thyroid of the rabbit are quite large, and contain relatively few faintly argyrophilic granules in their cytoplasm. They arise in large numbers in the thyroids of young rabbis, and after they lose contact with the colloid contained within the follicles they migrate into the interfollicular spaces. The possible rôle of the parafollicular cells is discussed. It is concluded that the cells under consideration do not produce colloid, and that they are not the source of new follicles, as recently suggested by Zechel ('31, '32), who has found them in the thyroids of dogs stained with the routine methods. They are elements either endowed with secretory capacities or else they represent a type of cell which, after absorbing substances from the colloid, transfer them into the blood stream through the capillary walls.—Author's Abst.

The size and shape of heart in goiter. Parkinson, J. and H. Cookson, Quart. J. Med. **24**: 499. 1931.

A consecutive series of 130 patients with goiter causing symptoms was examined with the primary object of deciding the size and shape of the heart by radiography. In addition a series of post-mortem records of 43 goiter cases was investigated to determine the incidence and distribution of cardiac hypertrophy. Of the 43 cases of goiter all but three had shown the classical symptoms of thyroid intoxication. There proved to be hypertrophy of the heart in rather more than one-half. The increase involved both ventricles as a rule, sometimes the left, more than the right, occasionally the left alone. A predominant or isolated hypertrophy of the right side was never seen. In general it was the younger patients and those with the shorter duration of symptoms who showed no hypertrophy. It was also in the younger patients (under 30) that the rhythm had been normal throughout or fibrillation had come only as a terminal event. Established fibrillation occurred in older people with an average age in eight cases at death of 51 years. The heart weight was greater on the average in those with established fibrillation than in those with normal rhythm. The greatest increase in heart-weight was found in those with fibrillation and heart failure. When emaciation was extrame, the heart was only slightly or not at all hypertrophied. Clinical and x-ray observations were made on 130 patients with goiter and symptoms from it. Enlargement was found in about 45% of the cases, usually slight or quite moderate, but not rarely great. In most it involved both contours of the heart, but more particularly the left, and sometimes the left only. The incidence of auricular fibrillation, including both paroxysmal and established forms, was 27%. Heart failure was present at some time in twelve, and all these had fibrillation, except one with a complicating hypertension. The form of the heart is often affected in a characteristic way in goiter. Undue prominence of the pulmonary arc was a striking feature of about one-third of the series, sometimes appearing as a convexity on the left profile, sometimes combining with an enlargement of the heart to the left to render this profile straight. An exaggeration of this arc is often an early change, preceding any enlargement of the heart chambers. Post-mortem measurements showed that the pulmonary artery was often dilated. The left auricle was not enlarged out of proportion to that of other chambers of the heart—a sharp distinction from the heart of mitral stenosis. The superior vena cava was sometimes prominent; this would be expected with the venous congestion of heart failure, but such an explanation only applied to a small proportion. The aortic arch reached too high a level in the chest in about one-third. The form of the vascular pedicle was modified occasionally by a retrosternal goiter. When symptoms are mild or of short duration the heart in goiter is normal in size and shape. When symptoms are severe and of long standing it is in a fair proportion both enlarged and modified in shape. The greatest enlargement is seen with auricular fibrillation and failure. The special form characteristic of the goiter heart is based upon a combination of prominence of the pulmonary arc, of the left ventricle, and to a minor extent of the right auricle. As a result of these changes, the heart may be generally enlarged, the contour retaining much the same shape as the normal heart,

whereas almost all other forms of cardiac disease causing enlargement greatly modify the shape. In their fully-developed form changes in the left arcs produce a distinctive picture with its straight left border and a right auricular arc only slightly enlarged. The heart so disposed, when seen from in front, has some resemblance to a ham. This picture differs from that of mitral stenosis in the relatively slight prominence of the right auricle and the fuller aortic knuckle as seen from the front, and in the absence of left auricular enlargement as seen from the front, and in the absence of left auricular enlargement as seen in the first oblique position. It approximates more to the cardiac outline of combined mitral stenosis and aortic incompetence. Radiological examination is a help in judging the presence of severity of a cardiac lesion in a patient with goitre. The demonstration of cardiac enlargement is important from the standpoint of the surgical treatment of goiter. When present, it is an added reason for, rather than a contra-indication to, surgical treatment. Though the greater the enlargement, the poorer is the prospect of a complete return to normal, yet the aid of surgery will often be required to check the progress of the lesion. In deciding the cause of obscure cardiac symptoms or enlargement, or of auricular fibrillation with or without failure, the discovery of the characteristic radiographic picture may suggest a goitrous etiology.
—Authors' Summary.

The thyroid gland and the vegetative nervous system (Ueber Beziehungen der Schilddrüse zum vegetativen Nervensystem). Pick, E. O., Deutsche. med. Wchnschr. **57**: 1532. 1931.

The regulation of temperature and the genesis of fever, functions of the vegetative system, are in close connection with the thyroid. Thyroidectomized animals do not withstand the lowering of temperature well. They do not react to pyretics (tetrahydronaphthylamin). The thyroid acts in two ways, first, directly on tissues and secondly indirectly through the central nervous system. Thyroxinized animals show a strong reaction to pyretics and cocaine and for this reason it is dangerous to use cocaine therapy in exophthalmic goiter and hyperthyroidism. The high temperature can be regulated by chinin, which acts as an antagonist of thyroxine directly in the tissues. Some hypnotics, derivatives of the barbituric acid, depressing the action of the stimulated vegetative centers, are beneficial to the thyroxine-treated animal. The author explains the refractory reaction of epileptics and encephalitics against thyroxine as a lesion of the vegetative centers.—E. Kodicek.

Thyroid and gonads in rooster feathering (Der Einfluss der Hoden bei der Wirkung der Hyperthyreoidisierung auf den Geschlechtscharakter des Gefieders beim Geflügel). Podhradsky, J., Endokrinologie, **7**: 241. 1930.

Thyroid feeding of castrated roosters produces changes in typical male feathering, more largely related to color intensification, width and length. The action appears to be complementary to the testis, but independent; perfect feathering being due to the hormone activity of both glands.—B. C.

The occurrence of parafollicular cells in the thyroid of the rabbit. Raymond, Natalie, Anat. Rec. **53**: 355. 1932.

In rabbit thyroids prepared with the Cajal silver-impregnation method it has been possible to trace the development of parafollicular cells. With routine hematoxylin-eosin staining these cells could only be detected and were not available for study. Parafollicular cells have been recognized in dog thyroids and have been considered a second epithelial component of mammalian thyroids. In the rabbit they differ markedly from the ordinary follicular cells in that they are very large and clear, and the cytoplasm contains scattered moderately argyrophilic granules of different sizes; there is no marked nuclear differentiation. Parafollicular cells originate in the follicular epithelium, migrate from their original position, and come to lie outside the follicle. Due to the closely surrounding layer of connective tissue usually found in the rabbit thyroid, they are often closely pressed against the follicle from which they arose and markedly distort it.—Author's Abst.

Status thymolymphaticus and lymphaticus in goiter and Basedow's disease (Status thymolymphaticus bzw. lymphaticus bei Kropfträgern und bei Basedow). Roth, S., Endokrinologie, **10:** 58. 1932.

A statistical study of the relationship of status thymolymphaticus to simple goiter and Basedow's disease was undertaken in order to determine to what extent status thymolymphaticus can be considered as the cause of fatal outcomes, which follow some thyroidectomies. Autopsy records were studied (1590 subjects). In 814 cases or 51.19% there was enlargement or changes in the thyroid gland. (Goiter is a frequent occurrence in Freiburg.) Considering the 71 congenital cases as a separate group the author found in the remaining 743 cases, 239 cases or 32.17% with diffuse enlargement of the thyroid and 504 cases or 67.83% of the nodular type. He came to the following conclusions: (1) The so-called status lymphaticus or status thymolymphaticus is not more common in individuals with simple goiter than it is in individuals without. The changes in the thyroid gland in simple goiter have no influence on the development of status lymphaticus. (2) In cases of Basedow's disease, status lymphaticus or thymolymphaticus was found to be very common, almost a rule. Simultaneous involvement of the thymus is not present except in old people or under certain circumstances such as endocarditis. (3) The changes in the thyroid gland in Basedow's disease, the status thymicus and the lymphatismus are independent conditions brought about by the same factor which causes Basedow's disease.—A. Rudy.

Thyroid-forming potencies of the early chick blastoderm. Rudnick, Dorothea, J. Exper. Zoöl. **62:** (No. 2). 1932.

Chorio-allantoic grafts of right, median, and left pieces of the anterior end of the area pellucida of chick blastoderms at stages of the definite primitive streak and head process were studied with reference to the occurrence and differentiation of thyroid tissue. In the earlier of these stages, thyroid is found in grafts of both median and lateral pieces; in those from lateral pieces, only after the head fold has appeared. These results may be interpreted as showing lateral separation of two distinct centers originally near the median line, or bilateral localization of what was in the beginning a single broad field. Potential thyroid at these stages is, by all indications, not indifferent, though a capacity for self-differentiation has not been demonstrated. Examination of grafts of the thyroid anlage of the seventy-two-hour chick shows it to be a self-differentiating system by this stage. Thyroid in grafts from definite primitive-streak stages shows a unique capacity for differentiation accelerated as compared with normal thyroid of corresponding age. This acceleration is less marked in grafts from the head-process stage, and is not present in seventy-two-hour material. This may be interpreted as progressive fixation of differentiation rate in this tissue.

Exophthalmic goiter with low basal metabolic rate. Troell, A., Hygiea, **94:** 45. 1932. Abst., J. A. M. A. **98:** 1608.

In 14 cases of thyrotoxicosis with a metabolic rate lower than plus 20%, 12 presented the microscopic picture of a diffuse exophthalmic goiter and two were nodular goiters with the pathologic-anatomic picture of simple colloid goiter, the one, however, with practically all clinical symptoms of thyrotoxicosis. Troell says that, while these cases in no way lessen the requirement for examinations of the basal metabolism as a dominating factor in the diagnosis of toxic goiter, they show that a laboratory test alone cannot be decisive for the clinical diagnosis. Establishment of the diagnosis of thyrotoxicosis in these cases calls for pathologic-anatomic examination of the thyroid. Whether or not operative treatment is rational in cases without a certain pathologic-anatomic rate, only experience can determine.

The occurrence of seasonal variations in the goiter of rabbits produced by feeding cabbage. Webster, B., D. Marine and Anna Cipra. J. Exper. Med. **53:** 81. 1931.

The evidence presented indicates that cabbage maturing in the spring and summer months has little goiter-producing power. Cabbage maturing in the late autumn has much greater goiter-producing power, although this shows considerable variation in different years. It has not been possible to correlate available meteorological data with these variations.—Authors' Summary.

Blood cholesterol in experimenta hypo- and hyperthyroidism. Westra, J. J., and M. M. Kunde. Proc. Soc. Exper. Biol. & Med. **29**: 677. 1932.

Changes in blood cholesterol in both clinical and experimental hypothyroidism and hyperthyroidism have been reported recently by several workers. Briefly stated, hypothyroidism is accompanied by an increased blood cholesterol; hyperthyroidism by a decreased blood cholesterol. This study was undertaken to confirm these findings in experimental hypothyroidism and hyperthyroidism in rabbits, and to see if any correlation exists between cholesterol changes and changes in the number of red blood cells and Hb. The technique for preparing cretin rabbits has been previously cited. Blood counts were made in the usual way; Hb was determined colorimetrically and is expressed in gm. per 100 cc. blood. Cholesterol was determined on whole blood by Sackett's modification of Bloor's method. All determinations were done in duplicate. Three cretin and 6 normal animals were used in the first series. These were fed from 0.318 to 0.59 gm. desiccated thyroids daily for 2 or 4 weeks. Thyroid feeding caused a decrease in the cholesterol of all rabbits of this series, but this decrease is not accompanied by a consistent change in the number of red blood cells or in Hb. A second series was studied, using 2 cretins and 4 of the animals in series I. After thyroid feeding, the losses of weight and the decreases in blood cholesterol of the 2 cretins are almost identical. There is no corresponding change in red blood cells and Hb. In the 4 normal animals, the weight loss is again roughly uniform, but again, there is no corresponding change in cholesterol and in red blood cells or Hb. Experiments indicate that the changes in blood cholesterol which follow thyroid feeding in both cretin and normal rabbits, show no correlation with changes in the number of red blood cells, or the amount of Hb.—M. O. L.

The respiratory metabolism in infancy and in childhood, the effect of thyroid therapy on the metabolism of protein in normal infants. Weymuller, L. E., T. C. Wyatt and S. Z. Levine. Am. J. Dis. Child. **43**: 1544. 1932.

A combined study was made of the respiratory metabolism and of the nitrogen elimination in the urine of normal infants preceding, during and following the administration of thyroid extract. The results show that the calorigenic action of the hormone in these subjects is ascribable to an accelerated combustion of three food-stuffs, protein, carbohydrate and fat. No evidence was found of a "toxic destruction" or of an excessive combustion of protein. The latter is, therefore, not usual or a necessary accompaniment of the calorigenic action of the thyroid hormone in normal infants.—M. B. G.

The respiratory metabolism in infancy and childrood, the calorigenic action of thyroid extracts in normal infants. Wyatt, T. C., L. E. Weymuller and S. Z. Levine, Am. J. Dis. Child. **43**: 845. 1932.

Thyroid extracts, in adequate dosage, exert a calorifacient action in infants with apparently normal thyroid glands and often induce in these subjects clinical symptoms characteristic of spontaneous hyperthyroidism. The metabolic response of these subjects to thyroid extracts in smaller dosage is inconstant. The minimal amounts of the drug capable of producing profound clinical and metabolic reactions in infants without hypothyroidism are apparently comparable to the dosage required to induce a similar response in adults without hypothyroidism. They notably exceed the usual dosage effective in subjects of all ages with hypothyroidism. The usual persistence of thyroid action in these normal infants was approximately two to three weeks. This time interval coincides with the usual duration of thyroid action reported for normal adults and is considerably shorter than the persistence of such action in subjects with hypothyroidism. In terms of absolute dosage, the whole gland product and the desiccated extract vary markedly in their potency as calorigenic agents, but they are equally potent when judged by their iodine content. On the latter basis, thyroxine, the active principle of the thyroid hormone, appears to be the most potent calorigenically of the three products.—M. B. G.

Hypothyroidism without myxedema. Youmans, J. B., and S. S. Riven, Ann. Int. Med. **5**: 1497. 1932.

Five illustrative cases are reported in support of the conclusions that hypothyroidism without myxedema is a more common condition than is generally appreciated and is not confined to regions where goiter is common. Failure

to recognize the disease is due to the vague symptomatology and to the fact that the signs and symptoms of the better known hypothyroid state, myxedema, are lacking. The diagnosis depends largely on the detection of an abnormally low basal metabolic rate, but this observation must be interpreted with caution since all low rates are not due to hypothyroidism. In diagnosis, the nature of the response to thyroid substance, which is specific in true hypothyroidism, is of great importance and serves to distinguish between lowered metabolic rates due to hypothyroidism and those due to other causes.—R. G. H.

Cellular studies on the thyroid gland. Zechel, G., Surg., Gynec. & Obs. **54**: 1. 1932.

In addition to the common cell in the thyroid gland, there is found a second less frequent type which is situated mostly in the interfollicular cell groups and only rarely in the follicular wall. This cell is larger than the common cell, has a large nucleus and stains brightly with eosin. It seems to be of epithelial origin. Frequently small groups of these large cells are located closely to gaps in the walls of follicles undergoing disintegration. The large cell is more numerous in the juvenile and regenerating gland. In its function it seems to be associated not only with production of colloid but also with the formative changes of the gland.—Author's Abst.